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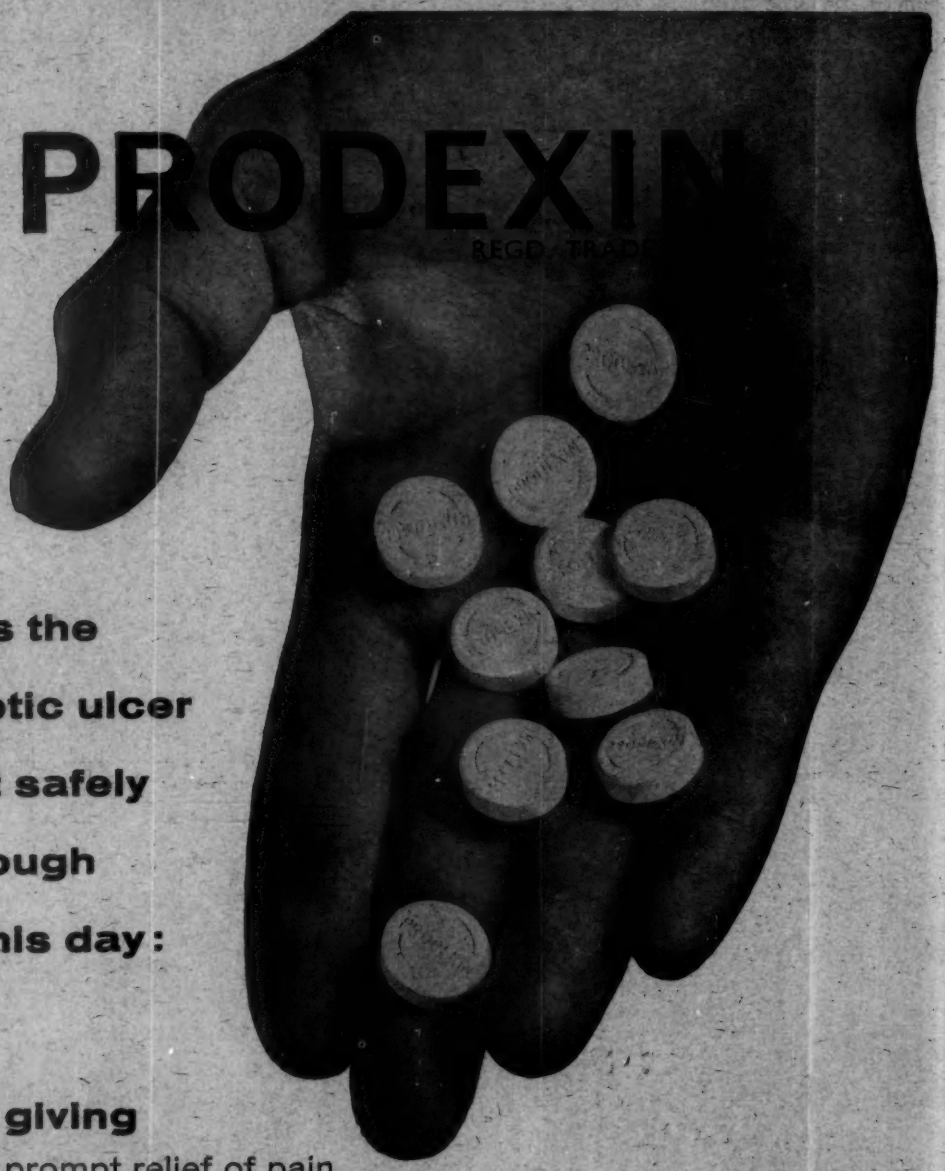

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BRITISH MEDICAL JOURNAL

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THE ENDOCRINE ORCHESTRA*

BY

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For we are members one of another.—Eph. iv. 25.

Sir Walter Langdon-Brown (1931) was the first to write that "the pituitary is the leader in the endocrine orchestra." This phrase has been frequently misquoted, and not infrequently criticized. You will observe that he referred to "the leader *in* the endocrine orchestra," having in mind the pituitary as the first fiddle and not as the conductor. If we wish we may still reserve the rostrum and the baton for the hypothalamus. He was careful not to carry his picturesque analogy too far, and we shall be wise to follow his example. Aphorisms and analogies do something to decorate the plain face of science, and if they make the lady more attractive to the neophyte, then they serve their turn.

The metaphor was apposite enough in 1931 when Langdon-Brown first employed it. Smith (1930) had recently reported that the removal of the pituitary in the rat resulted in dwarfism and sexual immaturity, but that normal growth and development was restored by pituitary transplants. Evans and Simpson (1928) had isolated a growth hormone from the eosinophil cells. Harvey Cushing (1930) had just delivered the Lister Memorial Lecture in which he provided a group of clinical pictures which illustrated these results of animal research.

Langdon-Brown came to this new knowledge with a mind long prepared. In a fragment of autobiography which he wrote for his wife in 1932 he tells of his undergraduate work at Cambridge:

> "In the Easter vacation I applied for permission to stay up and work at embryology by myself. I incubated hens' eggs, stopping their growth at different stages and laboriously cutting microscopic sections of the embryo in long ribbons and then mounting them on slides. Day after day, the whole day, hardening in preservatives, staining, cutting, mounting and then drawing my sections. The quiet, glowing happiness of it all comes back as I write. Gradually to see the brain, the backbone, the eyes, the heart forming themselves before my eyes. I could hardly tear myself away from this self-imposed task. I can still recall the thrill as I saw—what had not then been described—the pituitary arising like a nephridium which, according to a theory I was already formulating, it ought to do. I remember drawing a diagram on the laboratory benches before a group of fellow students to illustrate the idea of the evolution of the ductless glands (whose functions were then quite unknown) which was surging in my brain."

Langdon-Brown's intellectual range, both inside and outside medicine, was unusually wide, but in the twin fields of the autonomic nervous system and the endocrine system he maintained a constant interest. He was always fascinated by the influence of the emotions on these two systems, and in the last twenty years of his life he was very occupied with the importance of psychological factors in the production of physical ill-health. When I was asked to deliver this Langdon-Brown Lecture I was therefore naturally attracted by the subject of the influence of emotional factors on the control and function of the endocrine system. Experimentalists have, however, in this generation been mainly concerned with the hypothalamus, the pituitary, and the hormones themselves, and a relatively small amount of time has been given to the exploration of the extensive neural connexions of the hypothalamus with the cerebral cortex, the basal ganglia, and the thalamus. New analytical techniques are now being developed (Mason, 1959) which will eventually map out this enormous field, and, although the early results undoubtedly indicate that these higher centres have a profound effect in modifying hormonal output, I decided that it would be premature to try to review the relations of the nervous system with the endocrine system. I must hope that some successor of mine in the Langdon-Brown Lectureship will embrace an opportunity which no one would have seized more eagerly than Langdon-Brown himself.

There is, however, one area of the brain outside the hypothalamus in which hormonal control has been shown to be located, and this is the posterior diencephalon-pineal region. Gordon Farrell (1959, 1960) and his colleagues, by a series of comprehensive and brilliant researches, have established that this area secretes a hormone (first called "glomerulotrophin," but now named "adrenoglomerulotrophin" in response to the protests of sensitive nephrophils) which controls the secretion of aldosterone from the zona glomerulosa of the adrenal cortex. Destructive lesions in the mid-brain of cats show that a large area, lying inferior to the central grey substance and between the substantia nigra on both sides, is concerned with the regulation of aldosterone production. Experiments with extracts of beef brain have, however, demonstrated that the pineal gland produces the most potent extract in the production of aldosterone from the zona glomerulosa of the adrenal cortex. Further research is suggesting that there is also an inhibitory component in the pineal complex (Farrell, 1960). Langdon-Brown would have been fascinated by this new-found function for the pineal

*The Fourth Langdon-Brown Lecture delivered at the Royal College of Physicians of London on November 17, 1960.

gland, for he often referred (1922) to Gaskell's conclusion that the pineal gland was all that remained in the higher vertebrates of the pair of median eyes in arthropods, one of which exists still in the larval lamprey, the immediate ancestor of the lowest vertebrates. How delighted, too, he would have been by Farrell's speculative comment in the discussion at the Laurentian Hormone Conference of 1958:

"The pineal organ has been regarded by some embryologists as a degenerate eye. I wonder if this organ is an electrolytic receptor of some kind? I think it would be a most intriguing study. Simple forms of aquatic life might have need for an 'eye' which can detect the sodium content of the water. You can imagine such an animal swimming along the shore and coming to a fresh-water stream in which he isn't prepared to live. An electrolyte-sensitive structure may detect the fresh water, and the animal goes the other way. On the other hand, if he wants to go into fresh water he'll know where to go. It would be a lot of fun to study this; it sounds as though it's worth a summer at Wood's Hole." (Farrell, 1959.)

Langdon-Brown continued throughout his life to relate his biological knowledge to the development of the endocrine system. He wrote on one occasion: "The mesomatic coxal glands of the arthropod ancestor gave rise to the thyroid, parathyroids and thymus . . . the thymus arising from the dorsal side of the gill slit, and the parathyroids from the ventral side" (Langdon-Brown, 1922). He would have been happy to read of the support which his nephew, Sir Geoffrey Keynes (1954), has given to the theory of an endocrine activity for the thymus.

I shall consider now what has been learnt of the control of the anterior pituitary hormones by the hypothalamus, mentioning first the portal system of the hypothalamus and the hypophysis.

Hypophysial Portal System

Harris (1955) has been foremost in maintaining that the hypophysial portal system carries humoral substances from the hypothalamus which regulate anterior pituitary activity. This hypothesis is now generally accepted. The anterior pituitary, like the liver, has not only an arterial blood supply and venous drainage but a portal system also. These portal vessels take origin in the median eminence of the hypothalamus as a primary plexus of capillaries which join together to form small trunks that run down the infundibular stalk to the anterior pituitary.

Sections of the pituitary stalk which divide the portal vessels result in atrophy of the target glands—gonads, thyroid, and adrenal cortex—and when the portal vessels regenerate there is a return of pituitary function.

Nikitovich-Winer and Everett (1958), working in Harris's laboratory, have made the crucial experiments. They transplanted the anterior pituitary under the capsule of the kidney, and then, after some weeks, placed it under the median eminence of the hypothalamus. When the transplant was again well vascularized by the portal vessels, activity was largely restored to the atrophied endocrine organs. When a similar graft was placed beneath the temporal lobe endocrine function was no better than it had been when the graft was in the kidney.

Hypothalamic Control of the Anterior Pituitary

The hypothalamic control of the anterior pituitary has been investigated in many animals by three experimental techniques. In the first, the pituitary is transplanted, as we have seen, to other sites in the body, such as the eye and the kidney; in the second, destructive electrolytic lesions are selectively placed in different regions of the hypothalamus; and, in the third, various areas in the hypothalamus are stimulated by unipolar or bipolar electrodes left in position for several weeks. In all these experiments the results are usually assessed, not by direct measurement of the trophic hormones from the anterior pituitary, but indirectly by changes in the target organs.

The object of the transplanting experiments is to define the degree of dependency of the five trophic hormones — follicle-stimulating hormone (F.S.H.), luteinizing hormone (L.H.), prolactin (L.T.H.), thyrotrophic hormone (T.S.H.), and adrenocorticotrophic hormone (corticotrophin; A.C.T.H.)—on the hypothalamus. A complex pattern of hypothalamic control emerges. The secretion of L.T.H. by the pituitary is autonomous, and it proceeds in regular fashion when separated from the hypothalamus (Everett, 1954, 1956). The secretion of the two other sex trophic hormones, F.S.H. and L.H., is entirely dependent on hypothalamic regulation (Harris, 1955; Greer, 1957). Thyroid function is greatly reduced, but a little autonomous activity remains (Brown-Grant *et al.*, 1957). The adrenals atrophy, but they still respond to what have been called "metabolic" stresses, such as laparotomy or the injection of adrenaline (Greer, 1960). We can summarize this experimental evidence in this way. For the regular delivery of the trophic hormones, with the exception of L.T.H., some hypothalamic agency is required.

Destructive lesions and electric stimuli have been used to discover the sites of hypothalamic control. Lesions in the median eminence, just above the infundibular stalk, cause gonadal atrophy, while in the anterior hypothalamus they produce an increased secretion of F.S.H. So that two areas for F.S.H. control are postulated, the one stimulating and the other inhibitory (Harris, 1960). Conversely, stimulating electrodes applied to the median eminence cause an increased secretion of L.H., while a destructive lesion in the anterior hypothalamus produces a diminished output of L.H. (Harris, 1960). For these reproductive trophic hormones, entirely dependent as they are on the hypothalamus for their release, there are then two centres—the one for braking, and the other for acceleration. This dual control has not yet been demonstrated for the other two trophic hormones, A.C.T.H. and T.S.H.

Let us assume that high levels of circulating oestrogen depress the stimulating centre, or excite the inhibitory centre, in the hypothalamus. What then passes down the portal vessels to the anterior pituitary to depress the release of F.S.H.? Is it a higher concentration of oestrogen than is already reaching the anterior hypophysis through the systemic arteries? Is the humoral agent an oestrogen, with some changed protein binding? Is there some other hormone secreted by the hypothalamus, specific for one trophic hormone, or common for several, such as vasopressin, which lies ready in the median eminence to play such a part? (For the hormones of the neurohypophysis, unlike those of the adenohypophysis, are actually produced in the hypothalamus.)

These questions which I have just posed for the gonadotrophins have been debated, too, for thyrotrophin. Harris and Woods (1958) have produced

evidence that vasopressin may act as the neurohumoral transmitter for thyrotrophin release, while Brown-Grant (1960) has suggested that the hypothalamus might act as a filter for thyroxine so that the anterior pituitary would receive blood of varying hormone content and respond by increasing or diminishing its output of T.S.H. This hypothesis has been adopted and extended by Purves (1960), who suggests that in the median eminence of the hypothalamus, or in the pituitary stalk, thyroxine is either destroyed or bound in a form which is relatively ineffective in releasing T.S.H. in the anterior pituitary.

It would have been pleasant to produce a less complex and better-defined account of the hypothalamic control of the anterior pituitary hormones. The brilliant experimental work outlined here has been done in the short space of ten years, and it is now possible to see that when the final picture emerges, although clarification will have been achieved, simplification is hardly possible. The experimentalist, engaged in constructing hypotheses and in devising experiments which may support or rebut them, must now and again be astonished that mechanisms so complicated are contained in an area so small as the hypothalamus.

The Ten Cerebral Hormones and Their Regulating Mechanisms

Most of us carry in our minds the simple notion of a servo feed-back mechanism which controls the relationship of the anterior pituitary and its target organs: "I ask for more, I get more; I need less and less is provided." More thyroxine is circulating and less thyrotrophin is secreted; less thyroxine is circulating and the output of thyrotrophin rises. This rigidity of homoeostasis is well suited to the constantly changing needs of the body, but it appears to be easily overthrown. For example, emotional stress in the rabbit causes a decreased output of thyroxine, and prolonged exposure to cold an increased thyroid activity, and neither of these effects is corrected by an altered output of T.S.H. (Brown-Grant, 1960). A similar situation occurs in disease, when the feed-back mechanism is transcended and the increased output of target hormones in Cushing's disease, and in thyrotoxicosis, is uncontrolled by the trophic hormones.

The feed-back mechanism does, however, exist, and the experimentalists have set themselves to answer the question: Where and how does it operate? The answers are not simple. The methods used are the injection of the target hormone, or the grafting of a fragment of the target gland, in the anterior pituitary or in selected areas of the hypothalamus. Ovarian fragments placed in the region of the paraventricular nuclei (anterior hypothalamus) reduce uterine weight, but they have no effect when placed in the anterior pituitary (Flerkó and Szentágothai, 1957). Oestrogen, which depresses F.S.H. output, stimulates the release of L.H. No feed-back mechanism is known for L.T.H.

Thyroxine is equally effective in suppressing the output of T.S.H., both in the anterior hypothalamus and in the anterior pituitary. It is probable that cortisol, too, operates both in the hypothalamus and in the pituitary to regulate the secretion of A.C.T.H., though this is still uncertain.

It should be remembered, here, that the production of other hormones is subject to different methods of regulation. The output of vasopressin is probably controlled both by the osmotic pressure of the plasma and by its volume (Van Dyke, 1960), while the stimuli for the production of adrenoglomerulotrophin, which regulates aldosterone excretion, include sodium depletion and a reduction in volume of body fluid (Bartter *et al.*, 1959). Growth hormone has not been included in this account, for we know nothing of its regulation.

I have summarized in Tables I and II what is known of the site of formation of these hormones—pituitary, hypothalamic, and pineal; the method of their regulation—nervous, chemical, or physical; and either their regulatory sites or their sites of action.

I have divided these hormones into two groups: in the first, those in which a feed-back mechanism from a target organ is established; and, in the second, those in which no feed-back mechanism has been established, and in which it may be assumed that the regulation of the rate of hormone production operates at the site of formation of the hormone. The unknown regulatory influences in the second group are nervous, chemical, and physical. Such additional mechanisms, as we have already seen, may operate also in the first group, and may indeed supersede the feed-back mechanism.

In Table I are included the trophic hormones with a feed-back mechanism, controlled by oestrogen, cortisol, or thyroxine, and all are formed in the anterior pituitary. The place of regulation is the hypothalamus in the case of the sex trophic hormones, and both the hypothalamus and the anterior pituitary in the case of T.S.H. and possibly also for A.C.T.H.

TABLE I.—*Cerebral Hormones With a Feed-back Mechanism*

Hormone	Site of Formation	Regulatory Mechanism	Site of Control
A.C.T.H.	Anterior pituitary	Cortisol	Anterior pituitary and (?) hypothalamus
F.S.H. L.H. (I.C.S.H.)	,, ,,	Oestrogen, progesterone, androgen	Hypothalamus
T.S.H. ..	,, ,,	Thyroxine	Anterior pituitary and hypothalamus

TABLE II.—*Cerebral Hormones Without a Feed-back Mechanism*

Hormone	Site of Formation	Regulatory Mechanism	Site of Action
L.T.H. ..	Anterior pituitary	Nervous	Breast, corpus luteum
Growth hormone	,, ,,	?	All somatic cells
M.S.H. ..	Pars intermedia	?	Skin
Oxytocin ..	Hypothalamus	Nervous	Breast, uterus
Vasopressin	,,	Plasma volume and osmotic pressure	Arterioles, renal tubules
A.G.T.H.	Pineal	Plasma sodium and volume	Adrenal cortex (zona glomerulosa)

In Table II are included the hormones without a controlling target hormone. Two, L.T.H. and the growth hormone, are formed in the anterior pituitary; one, the melanocyte-stimulating hormone (M.S.H.), is formed in the pars intermedia; two, vasopressin and oxytocin, are formed in the hypothalamus and stored in the posterior lobe of the pituitary; and one, adrenoglomerulotrophin (A.G.T.H.), is formed in the pineal gland. L.T.H. production appears to be controlled by nervous mechanisms, and its action is on the breast and the corpus luteum; the control of the growth hormone is as yet unknown, but is likely to be chemical, and its action is on somatic tissues; the control of M.S.H. is unknown, and its action is on the melanophores of the skin. The regulation of oxytocin

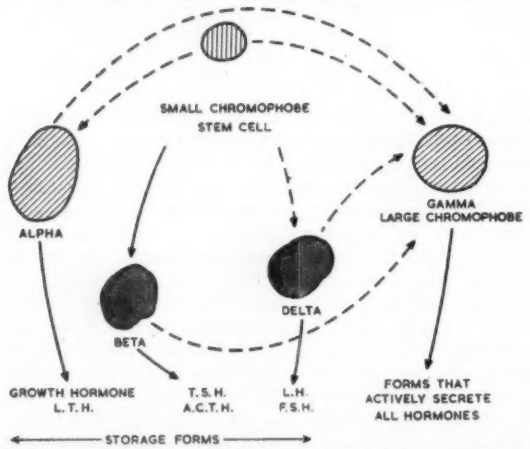
production is by nervous mechanisms, and its action is on the breast and the uterus. The regulation of vasopressin is by physical mechanisms, and its sites of action are the renal tubules and the arterioles. I have assumed that A.G.T.H production is controlled by chemical and physical mechanisms, and not by the output of aldosterone which it stimulates, its site of action being the zona glomerulosa of the adrenal cortex.

There are, then, ten known cerebral hormones; in four of them a feed-back mechanism has been demonstrated; in four their rate of output appears to be regulated by nervous, chemical, and physical influences; and in two the regulatory mechanism is unknown.

Cellular Origin of the Anterior Pituitary Hormones

Six hormones are formed in the anterior pituitary, and one of the puzzles about the histology of that organ has been that, in the past, only three types of cells were identifiable—acidophil, basophil, and chromophobe—and the last of these was regarded as inert. The introduction of periodic-acid-Schiff (P.A.S.) stains, with several modifications, has gone some way to solve these difficulties. P.A.S. stains carbohydrate in fixed tissues. Growth hormone and L.T.H. are simple proteins, and might be expected to be formed in P.A.S.-negative cells—and these are still the acidophil cells of the old nomenclature. F.S.H., L.H., and T.S.H. are glycoproteins, and the cells which produce them might therefore be expected to be P.A.S.-positive. A.C.T.H. is a polypeptide, but, since by clinical correlations it appears to be derived from P.A.S.-positive cells, it is suggested that it may have a carbohydrate-containing complex, but I have not been able to discover any chemical evidence for this suggestion. These P.A.S.-positive cells are the basophil cells of the old nomenclature, and types are variously described by different authors which may be the source, again by deduction from their disappearance or hyperplasia in different clinical states, of the sex trophic hormones, and T.S.H. and A.C.T.H.

The diagram shows the tentative scheme produced by one group (Ezrin *et al.*, 1958, 1959; Swanson and Ezrin, 1960). The small chromophobe cell is the stem cell, the acidophil cell (alpha) is the source of L.T.H. and growth hormone; two P.A.S.-positive (the red beta and the blue-purple delta) cells are the source of A.C.T.H. and T.S.H. and of the sex trophic hormones respectively; and the large lightly staining chromophobe, the gamma cell (which is the amphophil cell in Russfield's nomenclature) (Russfield *et al.*, 1956), is now regarded as an actively secreting cell from which all hormones may be formed. The most interesting suggestion for clinicians which emerges from these investigations is that the chromophobe adenoma is not the inactive tumour which it was formerly thought to be, but an adenoma in a state of ineffective activity—a new hypothesis which correlates well with recent clinical observations.



Normal anterior-pituitary-cell types stained by iron-P.A.S. technique. (From a diagram provided by Dr. Calvin Ezrin.)

The long-continued state of endocrine deficiency which often precedes the recognition of a chromophobe adenoma has puzzled clinicians. A woman patient of mine (Hubble, 1952) presented with impairment of visual fields at the age of 51, which was proved to be due to a large chromophobe adenoma. The endocrine associations of this tumour had been present for 40 years, for she had never menstruated and her height was 4 ft. 9 in. (145 cm.). Jefferson (1957) has suggested that these chromophobe adenomas develop because of an inability of the cells—what would be called to-day a defect in biosynthesis—to manufacture and appropriate trophic hormones. Van Wyk and Grumbach (1960) suggest that these chromophobe adenomas may develop in response to a failure of the target hormones. Either of these mechanisms may be operative, but where there has apparently been a very early failure of the growth and sex trophic hormones the Jeffersonian hypothesis provides an interesting and rational explanation, yet to be proved.

These modern descriptions, then, include five cell types, and, of these, three cells are each storing two hormones. It could be expected that two hormones derived from one cell might result in some overlap of function; or, alternatively, that when the cell was called upon to produce an excess of one of its trophic hormones the other might be deficiently formed. An example of the overlap in function is seen in the case of L.T.H. and the growth hormone, both of which are recognized in animals to have "mammogenic" and "galactopoietic" functions; and in man the not infrequent occurrence of galactorrhoea in association with acromegaly may be an illustration of this dual hormone effect.

There are several examples, too, both experimental and clinical, which may indicate a reversed relationship between the production of A.C.T.H. and T.S.H. This alternating production of T.S.H. and A.C.T.H. has been studied by Brown-Grant *et al.* (1957) in rabbits. The rabbit responds to experimental procedures known to increase the discharge of A.C.T.H. from the pituitary by decreasing thyroid activity. The thyroid response to stress is "thought to be due to a decrease in T.S.H. secretion coincident with the increased secretion of A.C.T.H. and perhaps consequent upon it" (Brown-Grant, 1960).

Interhormonal Relationships

There are many complex physiological relationships between the hormones, to which much attention has been given but with which I have not time to deal, such as the influence of the adrenal cortex on the sex hormones, the interaction of F.S.H. and L.H., and the synergistic effects of thyroxine and the growth hormone on growth.

Some hormones have overlapping actions, and these have recently been satisfactorily explained by the chemists. Oxytocin and vasopressin have long been known to have common pharmacological qualities, and it has now been shown that both are cyclic octapeptides whose only structural difference is in two amino-acids (Lerner *et al.*, 1960). The pigmentation which occurs in conditions in which excessive quantities of A.C.T.H. are secreted, such as Addison's disease and congenital virilizing adrenal hyperplasia, has now been proved to depend on the fact that melanocyte-stimulating activity is built into the corticotrophin molecule—there are 13 common amino-acids in the molecules of A.C.T.H. and M.S.H. (Li, 1957; Hudson, 1960).

There are, however, many pluriglandular syndromes occurring in man which cannot be explained by the near-chemical identity of pituitary hormones. Examples of these syndromes are the coexistence of thyrotoxicosis and diabetes, of thyrotoxicosis with Addison's disease, of acromegaly with thyroid and adrenal enlargement and galactorrhoea, of hypogonadism with thyrotoxicosis, of puberty in boys with gynaecomastia, of Klinefelter's syndrome with thyroid and adrenal adenomas, and of hypothyroidism in girls with precocious puberty and galactorrhoea. Considerable interest has also been aroused recently by syndromes in which multiple endocrine adenomas are present. The pituitary adenomas which develop after ablation of the adrenals may give rise to pluriglandular syndromes.

It is possible to speculate concerning the mechanisms involved, but we cannot hope, for example, to explain with certainty the not infrequent occurrence of thyrotoxicosis with Addison's disease until we understand the aetiology of both these disorders, and until routine assays of thyrotrophin and corticotrophin are generally available. As we have seen, Brown-Grant postulates in experimental animals an inverse ratio in the output of A.C.T.H. and T.S.H. which could be held to explain these phenomena in man. Of 538 patients seen at the Mayo Clinic (McConahey *et al.*, 1960) during 1913–58 suffering from Addison's disease, 16 (3%) had Graves's disease either before, during, or after the onset of Addison's disease. In 12 of the 16 patients Graves's disease appeared some time before the Addison's disease was apparent.

Van Wyk and Grumbach (1960) invoked the explanation of a "pituitary overlap" to account for the presence of precocious menstruation, galactorrhoea, absence of pubic hair, and enlargement of the sella turcica in three hypothyroid children aged 7, 8, and 12 years. All these abnormal signs disappeared with thyroid therapy, and the size of the sella turcica gradually reverted towards normal. The authors suggest that hyperplasia, and possibly adenoma, of the anterior pituitary existed in their patients, and associated with the presumed high output of T.S.H. there was an overlapping secretion of gonadotrophins and mammotrophic hormones. In a patient of mine—a cretin aged 25—there was overdevelopment of the penis, testes, and scrotum, again without any growth of pubic hair (Hubble, 1955).

This pituitary overlap could be explained by the non-specificity of the neurohumoral mediator coming down the portal vessels from the hypothalamus so that more than one anterior pituitary cell is stimulated to activity, a true hyperpituitarism (Hubble, 1955). In some of these syndromes the explanation may lie in the hyperplasia of the large gamma or amphophil cells which both Russfield and Ezrin believe to be capable of producing all the anterior pituitary hormones.

It might be expected that when the hormones which have a universal effect on cellular metabolism and growth—such as thyroxine and the growth hormone—are present, in deficiency or in excess, some evidence of this would be discovered in the function of other endocrine glands. This is becoming increasingly apparent.

For example, in hypothyroidism there is sometimes defective adrenocortical function as tested by urinary output of 17-OHCS and by A.C.T.H. stimulation (Hubble, 1955). Although conflicting reports have been published concerning the effect of thyroxine lack on the adrenal cortex, recent evidence establishes it beyond doubt (Felber *et al.*, 1959). Thyroxine deficiency may also affect pituitary function—myxoedema of the pituitary. The secretion of A.C.T.H. is reduced or deranged (Felber *et al.*, 1959), and the output of T.S.H. has occasionally been reported to be low and to be restored to normal or high levels by thyroxine therapy (Gilliland and Strudwick, 1956; Di George *et al.*, 1957). In the male cretin to whom I have already referred there was no gonadotrophin output in the urine when he was admitted to hospital, but with thyroxine therapy the output increased slowly to 6, 16, and, finally, to 18 mouse units/24 hours.

A more specific effect of growth hormone on the endocrine system will be no more than hypothetical until assays of growth hormone and treatment with human growth hormone are more readily available. Judging by the effects of acromegaly on the endocrine organs it is reasonable to suppose that the growth hormone has some effect on the parathyroids, the pancreas, the thyroid, the ovary, and the adrenal cortex. Harrison and Russell Fraser (1960) have advanced the theory (and given their reasons for believing it) that multiple endocrine adenoma syndrome (pituitary, parathyroid, and pancreas) is caused by an increased secretion of growth hormone. Dwarfs who are assumed to have a deficiency of growth and sex hormones—congenital hypopituitary dwarfism—may ultimately develop mild signs of hypothyroidism and hypoadrenocorticism (Hubble, 1957; Martin and Wilkins, 1958). I think this partial defect of the thyroid and the adrenal cortex may not be directly due to a defective production of T.S.H. and A.C.T.H., but may result from a lack of stimulation of these glands by the absent growth hormone.

I have suggested explanations for these pluriglandular syndromes, some now proved, others hypothetical. It will not be long, so concentrated is the work of endocrinologists and the chemists, before we have explanations for all of them based on fact.

The Parallel and the Model

It could be claimed that, while the organization of the endocrine system is more complex than that of the other systems (with the single exception of cerebral organization, of which we know comparatively little), our understanding of its working, though very incomplete, is yet more advanced than our knowledge of many somatic functions. Even such a cursory review as I have been able to make of the control and balance of endocrine mechanisms has given some idea of their

complexity. It may seem derisory, then, to return to Langdon-Brown's parallel of the orchestra as a model for the endocrine system. As a biological analogy, however, it has some meaning for us. An orchestra is a group of individuals harmoniously loyal to their higher control and playing with a common purpose towards a common end—the best possible interpretation of the piece of music in front of them. In the endocrine system is a group of individual organs, with much more complicated relationships and with controls which, although complex, are yet unified, working with a common purpose towards a common end—the maintenance of homoeostasis in the body.

I have looked in human affairs for a more appropriate analogy than the orchestra, but I have failed to find one. Man's social, political, and industrial organization, though a growth of many thousands of years, is but an embryo in biological evolution in comparison with the endocrine system. We may conclude, then, that, far from any of man's affairs providing an exact parallel for the endocrine system, the mechanisms of the endocrine system provide a model for man.

Langdon-Brown in his Maudsley Lecture delivered in 1936, and reprinted in his fine book of essays entitled *Thus We Are Men* (1938), discussed the biology of social life. He defined three phases of man's social evolution. In the first, individuality is at a discount and the community is held together by taboo and fertility rites. In the second phase, individualities develop and religious belief is towards individual salvation and personal immortality. We have not yet emerged into the third phase, in which the community works consciously, not instinctively as do the bees and the ants, and not without purpose aforethought as does the endocrine system, towards a common good. Langdon-Brown would have seen it as ironical, and yet not without hope for mankind, that the first hint of this conscious co-operation should have been, not for a common good, but for the avoidance of a common evil—the total destruction of man itself.

We would salute Langdon-Brown across the years as a devoted servant of this College, a fine physician, and in his time a pioneer of medical thought—and I part from him with this valedictory sentence which he chose for himself, "The life to which I belong uses me, and will pass beyond me, and I am content."

I am grateful to those who, by their discussions, have given me help in the preparation of this lecture. They include Dr. K. Brown-Grant, Dr. Calvin Ezrin, Dr. Melvin Grumbach, Professor G. W. Harris, Dr. R. L. Holmes, and Dr. Anita Mandl.

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MENTAL HOSPITAL INS AND OUTS

A SURVEY OF PATIENTS ADMITTED TO A MENTAL HOSPITAL IN THE PAST 30 YEARS

BY

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In 1957 Brill and Patton reported that between March, 1955, and March, 1956, there had been a fall of 452 in the population of the New York State mental hospitals. Since a steady rise of 2,000 patients a year had been expected to continue, this fall excited much interest. In 1959 the same authors showed that the decline had continued in the next three years by 453, 1,218, and 1,988 patients respectively, out of a total mental hospital population of 90,000. Kramer and Pollack (1958) were able to confirm that the decrease in 1956 was not confined to New York and that it was common to 39 of the 48 States. In that year there was a total drop of 7,400 in the mental hospital population of the United States. By the end of 1957 a further fall of 3,200 had been recorded.

Experience has been similar in England and Wales. The Annual Abstract of Statistics (1960) shows that the decline also began in 1955 and that by the end of 1959 there were about 15,000 fewer patients in mental hospitals than at the end of 1954, when a peak of 148,600 was reached. This fall had occurred despite a rising number of admissions. The decline has upset the calculations of the more gloomy prophets—for example, Norris (1959), who expected the mental hospital population to rise to 159,000 by 1960.

In Bexley Hospital in recent years the figures have followed the national trend, and the number of female patients has fallen from a peak of 1,284 at the end of 1954 to 1,165 at the end of 1959. One has had a strong impression that far fewer patients are "becoming chronic" and that this trend long preceded the introduction of the tranquillizing drugs in 1954, to which Brill and Patton (1957, 1959) attach primary importance. In order to try to check the reliability of this vague impression I have carried out an analysis of the duration of stay and the outcome of treatment for groups of patients admitted at various times in the past 30 years.

Material

The material under survey consists of the total intake of female patients for 1928–30, 1934–6, 1949–50, 1953, and 1957. The assessment of those admitted in earlier years was brought up to date in the last three months of 1959.

The inquiry was restricted to female patients for several reasons. The main one was that at that time I was working with them and knew at least half of the more recent admissions, and most of those who had remained from earlier years. In addition, there do seem to be such important differences between mental illnesses in men and women, in incidence, in age distribution, in manifestations and course, and perhaps even in ultimate prognosis, that they are best considered separately.

A study of length of stay and outcome has much more meaning if it is related to diagnosis as well as to sex, marital status, and such other information as is usually recorded in hospital registers. But diagnosis is a thorny problem in psychiatry. I have attempted to provide a retrospective diagnosis in every case, despite the risk that a knowledge of the outcome would influence one's diagnosis, and, like Shepherd (1957), I have used all the available records to try to arrive at a correct one. I was eventually able to find almost all the case-notes (see Table I). No patient whose notes did not come to light is still in hospital.

I began to collect data in April, 1957, and finished in January, 1960. Unfortunately, by the time I read Shepherd's (1957) monograph the investigation was well under way, and I could not modify it to include his valuable calculation of the total time a patient spent in hospital rather than the total number of times she was admitted.

Results

Although in setting out the results of this inquiry I have preferred to present them separated in broad diagnostic categories, there is some information covering the whole intake which may yield comparisons with other work (Table I).

1. The number of female admissions in a year has risen more than fourfold in 30 years, the number of first admissions threefold (cols. 3 and 6).

2. I have calculated the population at risk for the earlier years by dividing the total population of London by the number of mental hospital beds available, and then multiplying this number by the beds available in this hospital.

3. Readmissions have risen steadily and now form more than half of the total admissions (col. 6). Shepherd (1957) found that female first admissions fell from 68.5% of the total female admissions for 1931–3 to 58% for 1945–7.

4. Temporary patients. The figures in col. 8 confirm the view that this device for avoiding certification never proved very useful.

5. The notable fall in the proportion of single people probably reflects not only the general rise in marriage rates but also the rise in average age on admission (cols. 9 and 11). The "expected" figures for single people (col. 10) are derived from the census figures of 1951, which I applied to a population of these patients' age distribution.

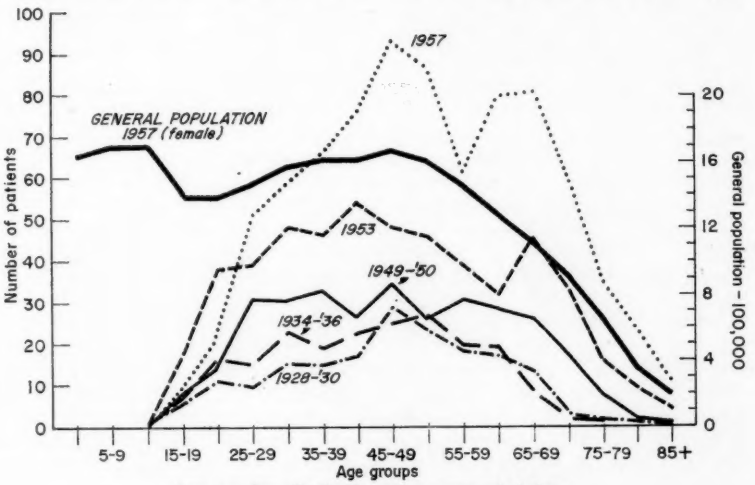

FIG. 1.—Age distribution of a year's admissions.

6. Lately, over a quarter of the female admissions are 65 years old or more (col. 11). Shepherd (1957) found that by 1945–7 a fifth of his female admissions were of this age.

7. Cols. 12 and 13 show the percentage and number from each year's intake who are still in hospital at the end of two years. The actual numbers have not changed very

TABLE I

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Years	No. of Female Admissions	Yearly No. of Female Admissions	Popn. of Catchment Area (approx.)	Missing Case-papers	First Admissions %	Voluntary Patients %	Temporary Patients %	Single %	"Expected" Single %	Aged 65 and Over %	Still in Hospital at End of 2 Years		Still in Hospital at Dec. 31, 1959	
											%	No. (per Year)	No. (from Each Year)	No. with Schizophrenia
1928–30	552	184	481,000	9	66·9	0	0	34·5		10·5	41·3	76	19	16·7
1934–6	621	207	437,000	6	66·5	16·3	3·6	38·9		5·3	41·6	86	28	23
1949–50	639	319·5	521,000	5	50·9	61·8	2·4	26·8	19·5	16·9	17·6	56	20	14·5
1953	516	516	593,000	1	50·7	75·7	1·6	26·6	20·9	20·9	12·4	64	23	11
1957	813	813	649,000	0	44·9	88·7	0·6	20·6	17·2	25·7	8·1	66	66	19

much, but because of the greatly increased total of admissions the proportion is much smaller. Col. 14 shows that more patients remain in hospital who were admitted in any year of the triennium 1934–6 than of those admitted in 1953.

Age Distribution.—This is illustrated in Fig. 1, in which it is also compared with the age distribution of the female home population for 1957 (*H.M.S.O., 1958*). Although the main bulk of admissions still comes in the fourth, fifth, and sixth decades of life, there has lately been added a large load of very elderly people. By 1957, 8.6% of the admissions were 75 years old or more. The median age of admission, which had fluctuated in the years from 1928 to 1953 between 45 and 48, rose in 1957 to 53.

Diagnosis. — No classification commands universal agreement in psychiatry, except perhaps as regards gross organic illness, and there is still widespread argument about such concepts as "reactive depression," "involutional depression," and "paraphrenia." I have used a very simple classification, but this has, of course, oversimplified the wealth of material encountered both in range and in diversity. There was a small group of patients' illnesses, mainly mixed endogenous and reactive depression, which resisted further classification. This group was larger in the more recent years. Table II and Fig. 2 show the total admissions for each period classified according to diagnosis.

Duration of Stay and Outcome.—These are illustrated for the complete series of patients in Fig. 3.

Schizophrenic Psychoses

I have included paraphrenia within this group, but the numbers of patients with this illness are separately listed in Table II.

Admissions for these illnesses showed a very steep increase by 1953 and again by 1957 (see Table II). Almost three times as many people were admitted with them in 1957 as 30 years earlier. This increase far exceeds that in the population at risk (see Table I), and might at first sight imply that many milder cases are now being admitted. Table III, however, shows

TABLE II

Diagnosis	Yearly Average			1953	1957
	1928–30	1934–6	1949–50		
Schizophrenic psychoses:					
Schizophrenia	31·0	36·3	36·5	68	92
Paranoid schizophrenia	15·0	20·3	19·5	32	53
Paraphrenia	23·3	18·0	16·5	29	44
Endogenous depression	46·0	53·3	104·0	157	296
Mania and hypomania	17·7	19·3	19·5	16	22
Manic-depressive depression	4·7	2·7	7·0	6	3
Reactive depression	1·3	9·0	23·5	35	51
Neurosis and personality disorder	0·3	6·7	33·5	67	94
Puerperal psychosis	5·7	7·0	9·5	17	20
Epilepsy	5·7	6·7	5·5	10	7
Organic psychoses:					
Senile and cerebral vascular	5·7	3·7	15·0	32	70
Alcoholic psychoses	6·7	5·0	3·5	5	1
Syphilis	7·7	4·0	1·5	2	2
Other organic psychoses	10·0	10·3	15·5	28	26
Other	0·3	3·0	6·5	11	32
Total	181·1	205·3	317·0	515	813

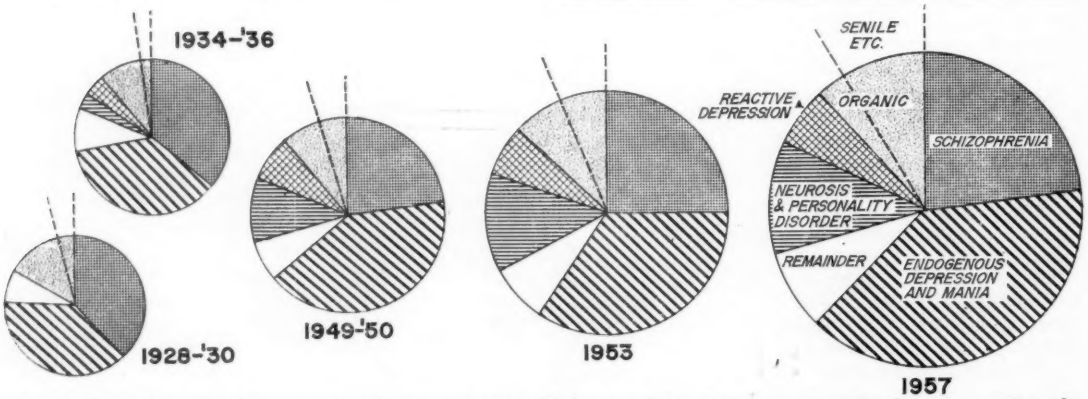

FIG. 2.—Admissions of various years according to diagnosis. The areas of the circles are proportional to the number of admissions.

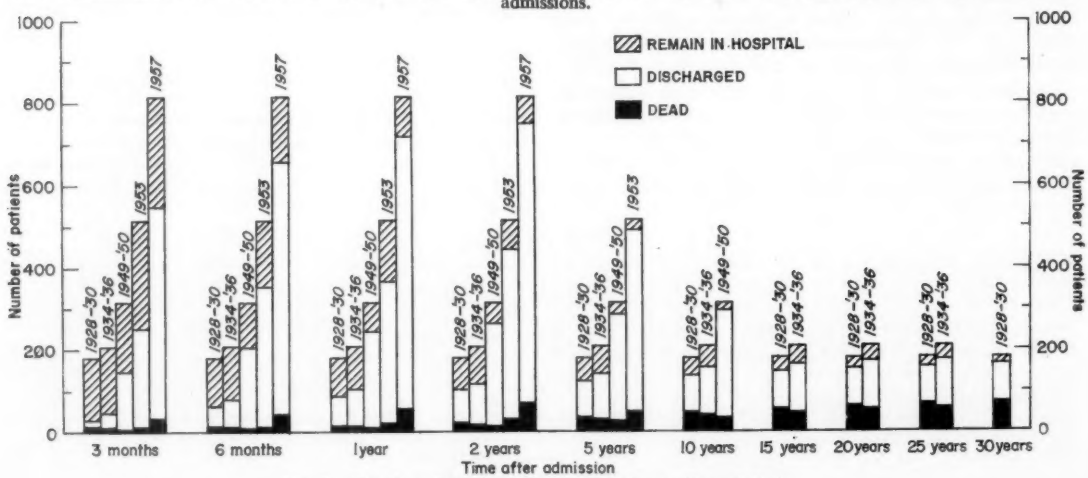

FIG. 3.—Deaths and discharges at various times after admission.

that the number of first admissions to a mental hospital for schizophrenia in 1953 was the same as it was 25 years before, and that even in 1957 their increase was modest—almost exactly in keeping with the increase in the number of people at risk. There has been a fourfold increase in the past 30 years in readmissions, and Table III shows that readmission much more often happens to-day within a year or so of discharge. The rising readmission rate cannot account for more than a small part of the increase in median age on admission, because this is now well

TABLE III.—*Schizophrenic Psychoses*

	Yearly Average			1953	1957
	1928–30	1934–6	1949–50		
Admissions	69	74·7	72·5	129	189
% certified	*100*	*89·8*	*61·9*	*33·1*	*23·3*
*% single**	*64·5*	*62·6*	*63·4*	*41·4*	*40·0*
Median age* (years)	27·1	29·4	30·6	30·9	38·5
Discharged recovered†	18·7	19·3	31·5	75	119
Median stay of discharges	7 mths	7 mths	6 mths	4·5 mths	9 wks
Still in hospital after 2 yrs	40·7	47	26·5	26	19
First admissions—total	46	49·3	34·5	47	61
" *	31	38	23·5	29	41
Discharged recovered†	8·7	10	10	22	24
Ever discharged	11·3	14·7	18·5	27	38
Still in hospital after 2 years	19·7	24·7	7	5	3
Median stay of discharges	10 mths	8 mths	5 mths	4·5 mths	8 wks
% already admitted in same or previous year	*8·7*	*8·9*	*12·4*	*12·4*	*15·5*
% readmitted in same or next year	3·8	*2·2*	*4·1*	*14·7*	*22·2*
3 or more previous admissions	1	2·7	8·5	23	54
Left against advice	0	1	6	14	27

* Excluding paraphrenics. † Or much improved.

over 30 even for first admissions. The only alternative explanation for the higher median age on admission to a change in age of onset of the disease is that more of the younger ones now go to the several other hospitals in South London which specialize in first admissions.

The extent of readmission has to be borne in mind in interpreting Fig. 4. This shows a great improvement in the outlook for the illness, or, at least, a much better chance of leaving hospital and a much shorter stay in recent years. In 1957 86.7% of the patients admitted with schizophrenia were out of hospital within a year compared with a meagre 26.5% 30 years ago. In fact, the duration of stay is not nowadays much longer than for those with affective psychoses.

By the end of two years only 19 (10%) of the schizophrenic admissions of 1957 remained in hospital, compared with 41 (59%) from a smaller general population 30 years ago (see also Table III). Shepherd's (1957) figures for female schizophrenics still in hospital after two years were 63% for those admitted in 1931–3 and 48% for admissions of 1945–7. Norris (1959) reported a comparable figure of 38% for admissions of 1947–9.

In this investigation only 12 of the patients admitted with schizophrenia in 1953 were still in hospital after six years; 25 years previously, at the end of the same period after admission, 35 were still in hospital. Nor is the outlook so completely hopeless, as is often supposed, for the patient who has been in hospital for more than three years. Altogether, in the years being considered, 42 such patients left hospital—a not inconsiderable number. Their years of discharge are scattered throughout the past 30 years, but 20 of them left hospital in 1955 and the years following. Most of these had responded well to chlorpromazine.

Some inroads seem, then, to be being made on the chronicity of the illness. Only three of the first admissions of 1957 were still in hospital two years later. A variety of causes may well have contributed to this outcome: the efficacy of physical treatments; the changed atmosphere of the hospital; and a readiness on the part of relatives and the community to accept improved patients at home without too much apprehension.

A corollary of all this is sometimes forgotten. Some attacks seem to clear up completely; other patients do not become completely well, and in their case a fresh attack of illness or altered circumstances may bring them back to hospital several times in the course of the illness. There seems to be no need to be disheartened by these frequent readmissions if they can be regarded as episodes in the long-term management of a patient who, if she had become ill 30 years ago, had only two chances in five (see Fig. 4) of ever being discharged. At least she is now at home and often at work for the greater part of the time.

A few further points from Table III are worth noting. There has been a steady fall in the proportion of certified admissions, which by now has fallen even lower. Secondly, the proportion of single people has fallen

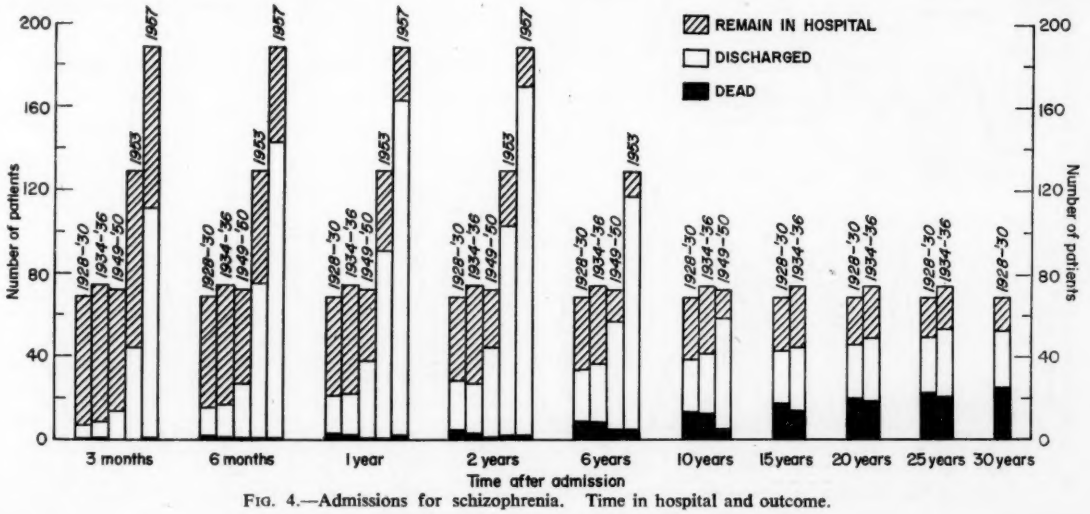

FIG. 4.—Admissions for schizophrenia. Time in hospital and outcome.

to 40%, which is nevertheless greatly in excess of the 18% or so one would expect in a population of this age distribution. Thirdly, only three of the first admissions of 1957 were still in hospital after two years, but of the admissions of that year a smaller proportion were discharged recovered or much improved than of the admissions of 1953. This, if confirmed, might suggest that both patients and doctors are somewhat too hasty in agreeing to discharge, which, however, is achieved far more quickly.

Deaths from Schizophrenia (see Fig. 4).—Patients now hardly ever die directly of schizophrenia. Of the 318 patients admitted with the disease in 1953 and 1957, only seven died during their stay; four were paraphrenics over 70 years old, and only one of the others died from causes connected with her mental illness. Of the 431 admitted in the six years 1928–30 and 1934–6, 50 have died, 26 of them from causes which seemed to be directly connected with their mental illness—exhaustion, tube-feeding, swallowing needles, scratching leading to sepsis, lodging of a crust in the throat, subdural haematoma from a fight.

Physical Treatment of Schizophrenia.—The results of this have been very difficult to assess, particularly from old case-records of patients one never knew. The results are expressed in Fig. 5. The newer forms of treatment have, of course, been given, as they become available, to the more chronic patients with some success. The amount of E.C.T. used in treating the admissions of 1953 may cause some surprise, as may the small numbers treated with deep insulin, but policies vary widely in different hospitals. For example, the hospital that Shepherd (1957) reported on was treating its 1945–7 patients three times more often with continuous narcosis than with E.C.T. The growth of E.C.T. and other forms of treatment is shown for the present series in Fig. 6.

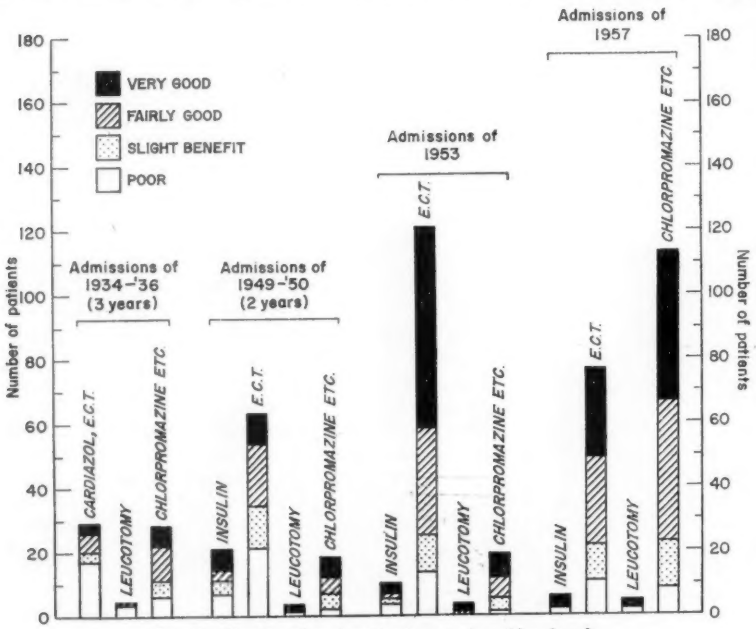

FIG. 5.—Results of various treatments in schizophrenia.

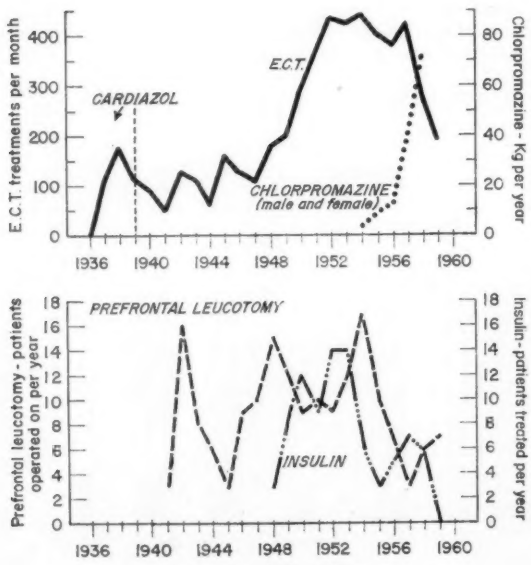

FIG. 6.—Physical treatment.

Endogenous Depression and the Manic-Depressive Psychoses

I have included involutional melancholia in this group. The findings are shown in Fig. 7 and Table IV.

Admissions for endogenous depression have shown a sixfold increase in the past 30 years. The actual number of patients with mania and hypomania has remained almost constant, however, and if allowance is made for the larger population at risk there seems to have been a fall in the prevalence of this illness. First admissions for this whole group of disorders have risen almost threefold.

TABLE IV.—*Endogenous Depression and Manic-depressive Psychoses*

	Yearly Average			1953	1957
	1928–30	1934–6	1949–50		
Admissions	68·3	75·3	130·5	179	321
% certified	*100*	*78·3*	*29·5*	*14·5*	*5·3*
Median age (years)	52·1	50·7	54·9	55·0	60·1
Discharged recovered*	40·7	44·3	110·5	144	272
Median stay of discharges	6 mths	5 mths	11 wks	10 wks	7 wks
Still in hospital after 2 years	19·7	22·7	10	15	13
First admissions	39·7	46·3	58·5	76	111
Discharged recovered*	21·3	27	50	58	93
Ever discharged	23·7	30·7	55	72	102
Still in hospital after 2 years	12	12·3	3	6	4
Median stay of discharges	6 mths	5 mths	11 wks	8 wks	7 wks
Aged 65 or more	6·3	4·3	7·5	21	30
% already admitted in same or previous year	*5·4*	*9·7*	*13·7*	*12·8*	*15·6*
% readmitted in same or next year	*3·4*	*3·5*	*7·3*	*15·7*	*25·5*
3 or more previous admissions	10	8	23	37	79
Left against advice	0	1	6	14	18

* Or much improved.

Even so the main increase, as with schizophrenia, has been in readmissions, often within a year or so of discharge. In fact, single admissions are the exception. Of the 130 admissions with these illnesses in 1950, only 36 (27.7%) had had no previous attack, and, so far as I could discover, no subsequent one. The corresponding figure for 1953 is 55 out of 179 (30.7%). The general impression, then (see Fig. 7 and Table IV), is of an improved recovery rate after a much shorter stay, but with a minimum of 40% of those discharged needing readmission within the next few years.

Some other points from Table IV are worth noting. The percentage of certified admissions is now very low indeed. The age of admission, even of first admissions, has risen lately, and 27% of the women admitted for the first time with these illnesses are now 65 years old or more. Discharge rates are very high indeed and have been high since at least 1949, particularly for first admissions; it is thus difficult to agree with Norris (1959) that "manic-depressive psychosis is an important contributor to the chronic population of mental hospitals," or that "these conditions have, in the long run, a bad prognosis." Only 13 of the admissions in 1957 were still in hospital two years later, and only 15 died. This, from an intake that included 55 people aged 70 years or more, seems on the face of it not at all bad. But readmission will be needed for 40%, according to Norris, in the next five years, and according to the figures from this hospital, necessarily less complete than hers, in the next six years. Yet readmission, if it does occur, carries the same favourable outlook for a short stay and a good outcome.

Deaths from Manic-Depressive Psychosis.—As with schizophrenia, it was by no means uncommon 30 years ago for the manic or depressed patient to die directly of the disease. Of those 431 manic or depressed patients who came into hospital in the six years 1928–30 and 1934–6, 131 have died, 45 of them from causes directly connected with their illness. On the other hand, of the 15 from the 321 similar admissions in 1957 who have died, 10 were over 70 and only three died of causes directly connected with their illness.

Physical Treatment of Endogenous Depression and Manic-Depressive Psychosis.—The median length of stay of those ever discharged has fallen in the past 30 years from six months to seven weeks, and the proportion leaving hospital within a year has improved from one-half to nine-tenths. The major part of this change occurred before 1949; that is to say, before all the administrative changes that have transformed mental hospitals in recent years were ever made. Although this investigation was not designed to show causes, the most probable explanation of the improved outlook and shortened stay is the success of E.C.T. Fig. 6 shows the changes in the main kinds of physical treatments used in Bexley Hospital in the last 20 years. Psychiatrists are often on the defensive about E.C.T. But if the alternative, as it was until recently, is a far longer stay in hospital, most patients realize that it would be foolish to reject it. By 1949–50 55% of the admissions for these illnesses were responding well to it. Of the 321 admissions in 1957, 252 (78.5%) were given it; 205 (81%) responded really well, and of these 49 (24%) needed more than a single course; those who did well were given an average of 9.5 treatments, but much the commonest numbers of treatments in a course were 6, 7, and 8.

Organic Psychoses

In the past 30 years patients admitted with senile and arteriosclerotic psychoses have increased twelvefold and now form one-twelfth of all admissions (Table V). Only about 10% are discharged, and this figure has remained unaltered throughout the period of survey. Of the demented patients admitted in 1957, 26 were over 80, a higher proportion of extremely aged people than in

TABLE V.—*Number of Patients with Organic Psychoses*

	1928–30 Average	1934–6 Average	1949–50 Average	1953	1957
Senile and arteriosclerotic dementia ..	5·7	3·7	15·0	32	70
Died in 3 months ..	0·7	0·7	3·0	5	19
,, ,, 12 ,, ..	2·0	1·7	4·0	11	32
Proportion that these form of all admissions of 65 or more ..	23·7%	22·9%	23·4%	26·8%	31·1%
Presenile dementia ..	1·7	0·7	2·0	3	5
Huntington's chorea ..	0·7	0·7	1·0	5	2
G.P.I.	7·7	4·0	1·5	2	1
Alcoholic psychoses ..	6·7	5·0	3·5	5	1
"Toxic-confusional psychoses"	3·7	2·0	1·5	2	3
Others	4·0	7·0	11·0	18	17
Total	30·0	23·0	35·5	67	99

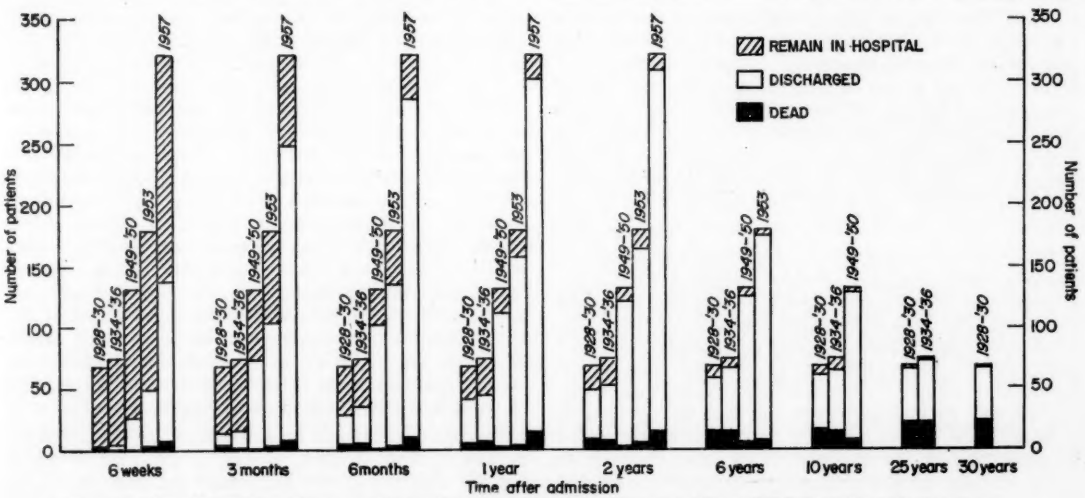

FIG. 7.—Admissions for endogenous depression and manic-depressive psychosis. Time in hospital and outcome.

earlier years. Despite the increase in senile and arteriosclerotic patients admitted, these illnesses still only account for less than one-third of the admissions who are 65 years old or more.

As is well known, there has been a falling off in admissions for G.P.I., but the decrease would probably be much more striking had male patients been included. The same holds good for alcoholic psychoses, but alcoholism leading to admission or complicating a depressive or psychoneurotic illness, though vastly less common in women than in men, does exist as a mental hospital problem. A minimum estimate for all 1957 admissions is that it complicated the picture in four and was the primary though non-psychotic condition in three more of the women.

A wide variety of psychoses secondary to known physical disease were encountered, and there was a residual group of toxic-confusional psychoses which at the time proved impossible to diagnose more accurately.

Other Conditions

The numbers in these residual groups are shown in Table II. They now amount to one-quarter of all admissions; 30 years ago they accounted for only 7% of admissions.

Puerperal Psychoses.—The proportion that these form of the total admissions has remained stable at about 3% throughout the period. It was reassuring to find that the last puerperal patient to die came in as long ago as 1942, and that the last one to become chronic and to be still in hospital was admitted in 1940. All the 20 admissions for this illness in 1957 had left hospital within three months; 14 of them had responded very well to E.C.T., often coupled with chlorpromazine. Of the 38 admitted in the earliest six years of this series, five died and three are still in hospital after 25 to 30 years.

Reactive Depression, Psychoneuroses, and Personality Disorders.—These groups, which now form more than one-sixth of the admissions, defy classification because they are overlapping categories. I have used the term "reactive depression" for those of good personality who had encountered severe stress. Only seven of those who came in in 1953 and a further seven in 1957 had had previous attacks outside the same and the previous year.

Mixed Depressions.—In this term are included illnesses that show both endogenous and reactive elements and often reveal neurotic personality features as well. They form a difficult group to treat because the presence of one group of factors militates against success in treating the other. E.C.T., for example, worked well in only about a third of them, but other aid, social or psychotherapeutic, was difficult to apply until the endogenous component of the illness had been tackled.

Roth (1960) says that neurotic illness beginning late in life is less uncommon than has hitherto been supposed. In this series about one in 15 of those with reactive and neurotic illnesses was 65 or over, but many of these had previously been admitted to hospital. In 1957 only six people over 65 were admitted *for the first time* with what seemed to be neurotic or reactive illnesses, in comparison with 30 for endogenous depressive disorders. It may well be that important physical and exogenous factors have played a part in precipitating many illnesses that I have assigned to the endogenous group because of the clinical manifestations, and that the figures from this series are not inconsistent with Kay's (1959) finding in his Stockholm material that three-quarters of the depressive illnesses of late onset had precipitating causes of these types.

"Hypochondriasis."—I could not escape this diagnosis for a few patients who seemed not to be suffering from a depressive, a paraphrenic, or a hysterical illness. It is a highly unpleasant condition. Of the 12 persons admitted with this diagnosis in 1957, only one of those discharged had made more than a slight improvement and three were still in hospital after two years.

Future Size of Mental Hospitals

The total number of patients remaining in hospital at the end of two years from the date of admission has not changed greatly in the last 30 years. It remains at about 65, though these are now the remainder from a much larger number of admissions than formerly. The diagnoses and age distribution of these chronic patients have, however, changed considerably (see Tables VI and VII). Schizophrenia has been replaced by the senile and arteriosclerotic psychoses as the most important cause of a stay in hospital of two years or more, and more than half of those who stay more than two years are 65 years old or more; in fact, almost one-third are aged 75 or over.

TABLE VI.—*Diagnosis of Those Who Stayed in Hospital More than Two Years (Percentages)*

Diagnosis	Year of Admission				
	1928–30	1934–6	1949–50	1953	1957
Senile and arteriosclerotic	4·6	2·7	14·4	22·5	30·8
Schizophrenia and paraphrenia	56·4	55·8	50·5	42·5	27·7
Depressive and manic	22·0	26·1	18·0	21·2	21·5
Other conditions	17·0	15·2	17·1	13·7	20·0
Total	100·0	100·0	100·0	100·0	100·0

TABLE VII.—*Age Distribution of Those who Stayed in Hospital More than Two Years (Percentages)*

Age—After Two Years in Hospital	Year of Admission				
	1928–30	1934–6	1949–50	1953	1957
Under 25	6·5	7·5	5·9	4·4	1·5
25–44	34·1	34·3	31·3	20·3	12·1
45–64	43·7	46·8	25·4	31·9	31·8
65 and over	15·8	11·4	37·3	43·5	54·5
Total	100·0	100·0	100·0	100·0	100·0

It seems likely, therefore, that, as the years go by and as the mass of young patients admitted in the 1920s and 1930s become elderly and die, the total number of patients in hospital will fall. This group of young and middle-aged patients is not being replaced. The number of patients still in hospital five years after admission has already shown a fall from an average of 60 from each year's intake 30 years ago to 23 for the admissions of 1953. The continued trend since then towards an older chronic population and the effects of the phenothiazine drugs would lead one quite reasonably to expect, therefore, that, even with no further advantages in treatment and no further changes in policy, beds will eventually only be needed for about one-third of the *chronic* population which we have at present. Many of the developments in the field of mental health that are being discussed at present will, if they are brought to fruition, further reduce the chronic population.

I have tried to form an estimate of how the number of female beds is likely to fall in the next 30 years, but the calculations are hazardous and rest on a large number of assumptions, which ignore the effects of any

of the changes in policy described above. The first is that the numbers admitted in future years will be the same as in 1957; in other words, no allowance is made for the effect on numbers of admissions of the increase in numbers of the population and the greater number of old people in it. The second assumption is that the discharges of future patients will follow recent experience. Thirdly, it is assumed that the expectation of life of those who will never be discharged is that of the general female population. There are, however, good reasons for supposing that their expectation of life is lower (Norris, 1959). Indeed, the "excess mortality" of mental hospital patients is much larger in the case of younger and middle-aged patients than of elderly patients—so much so that a prediction based solely on the ordinary expectation of life of the population in hospital on December 31, 1959, leads to the obviously unlikely conclusion that the number of patients remaining in five and ten years' time will actually increase.

In calculating the likely future population, therefore, I have used two methods. For those admitted in 1953 and before, I have projected the actual curves of discharge and death of these patients since that time (Fig. 8). These curves may be expected to meet at

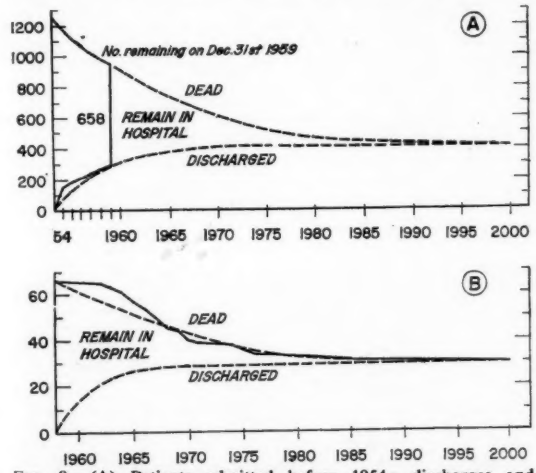

FIG. 8.—(A) Patients admitted before 1954: discharges and deaths 1954–9 and projection. (B) Admissions of 1957 still in hospital after two years. Projection of deaths based on expectation of life derived from age distribution (smoothed). Projection of discharges based on experience from 1949–50 and 1953 admissions.

about the year 2000, as the youngest patients in this group may be expected to die at about that time. For those admitted since 1953, with their high proportion of the elderly who stay more than two years, the "excess mortality" may well not be very great (Norris, 1959), and I have based the prediction upon the ordinary expectation of life. The error of this method in all probability leads to too high an estimate for the future hospital population, but how much too high I am unable to guess. One major difficulty in using an expectation-of-life method based on age was that I had to try to decide which patients were likely to be ultimately discharged so that I could know the ages of the remainder. I based these judgments on the patients' actual diagnoses and histories, and made use of information derived from the 1949–50 and the 1953 admissions to try to decide which actual patients were likely to leave after a spell of more than two years in hospital.

The predictions are contained in Fig. 8. This conservative estimate shows that *without any change in policy*, but, on the other hand, without allowing for a bigger population, total numbers may be expected to decrease by nearly 30% in 20 years, and that by then 38% of the patients will have come into hospital less than two years previously (compared with 27% now).

It has been estimated that up to 40% of the present population of this mental hospital would not need to remain here if there were alternative accommodation for many of the elderly and of the chronic mildly psychotic patients, and if welfare facilities were developed to enable others to live satisfactorily at home. If one assumes that 30% is a realistic figure for the reduction in total beds which developments of this kind will achieve in the next 20 years, the number of female beds needed then will be reduced to 592. If, in addition, beds are provided elsewhere, in psychiatric units attached to general hospitals and in medium-stay units for those whose illnesses last up to two years, a further reduction of 318 can be expected, leaving a long-term female population in 20 years' time of 274—less than a quarter of the present figure.

There can be many opinions about where psychiatric patients can best be treated, and about the load of mentally abnormal people which the community can be reasonably expected to bear in its midst; but there will be few who will mourn the disappearance of the vast mental hospital bequeathed to us by our grandparents.

Summary

This paper reports on the number, age, diagnosis, duration of stay, and outcome of all *female* admissions to one large mental hospital in the years 1928–30, 1934–6, 1949–50, 1953, and 1957.

The number admitted has risen fourfold and first admissions have risen threefold in 30 years, but the population at risk has only increased by one-third. Readmissions now form over half, instead of one-third, of the total admissions.

Over a quarter of those admitted are 65 years old or more, and one-twelfth are 75 years old or more.

Admissions for neurosis, personality disorder, and reactive depression have increased greatly and now form one-sixth of the total.

Three-quarters of those admitted in 1957 had been discharged within six months.

Although admissions for *schizophrenia* have increased threefold, this is wholly attributable to a rise in readmissions. The median length of stay of those ever discharged has fallen from seven months to nine weeks. Death directly from schizophrenia, once common, is now very rare.

Admissions for *endogenous depression and manic-depressive psychosis* have increased sixfold and first admissions threefold, but again the chief rise has been in readmissions. The median length of stay has fallen from six months to seven weeks; 85% of the admissions of 1957 had been discharged in six months. Admissions for *mania* have fallen.

Patients with *senile and arteriosclerotic dementia* account now for one-twelfth of all admissions; more than one-third of these in 1957 were over 80; only 10% are ever discharged.

Dementia has now replaced schizophrenia as the commonest cause of a stay in hospital of more than two years.

The decrease in the number of schizophrenic illnesses becoming chronic may well lead to a fall in the total patient population of 30% over the next 20 years. If, in addition, changes in national policy are effective, mental hospitals may perhaps be reduced to one-quarter of their present size.

I am indebted to the medical superintendents and other staff of 38 hospitals for help in tracing the progress of 124 transferred patients; and to Dr. J. A. Scott, Medical Officer of Health for London, and to the Town Clerk of Lewisham for help in calculating the population at risk.

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MULTIPLE-PUNCTURE VACCINATION WITH FREEZE-DRIED B.C.G. VACCINE IN SCHOOLCHILDREN

BY

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The value of B.C.G. vaccination of schoolchildren in this country in the prevention of tuberculosis has been sufficiently substantiated (Medical Research Council, 1956, 1959; Pollock, 1959; Springett, 1959) for it to require no further advocacy. There still remains, however, the problem of how it can be most effectively, rapidly, and economically administered to children, not only in this country but in those overseas countries with greater problems of tuberculosis control, expanding populations, hot climate, and insufficiency of public health personnel. For these countries a heat-stable freeze-dried vaccine which can be easily and efficiently administered would seem to provide the answer.

A freeze-dried vaccine for intradermal use has been prepared and used in Great Britain for several years, and reports on its efficiency in schoolchildren have been made by the Medical Research Council (1958) and by Alston *et al.* (1958). Although, in the strength issued at the time, the freeze-dried vaccine was slightly less effective than the fresh Danish, a slight increase in the bacterial content has eliminated this difference, and the advantages inherent in a freeze-dried vaccine have led to its widespread use.

Recently a stronger freeze-dried vaccine for multiple-puncture vaccination has been available, and reports on its use in schoolchildren have been published from Cardiff and Pembroke (Griffith, 1959) and from Rotherham (Hopper, 1960).

In February, 1959, a trial of this method of vaccination was initiated in four health divisions in north-east Cheshire. The aim of this trial was (*a*) to compare the results of multiple-puncture with intradermal vaccination, and (*b*) to make an attempt to assess some of the factors which influence the efficiency of multiple-puncture vaccination and thus to improve the technique or vaccine to such an extent that the degree of local reaction and allergy produced will compare favourably with those from intradermal vaccination.

First Trial (School Year 1958–9)

The object of this trial was to compare the effects of vaccine strength of 83 mg./ml. given by multiple puncture, using 20 needles at depths of 2 or 3 mm., with that produced by an intradermal vaccine of a strength of 500,000 viable organisms per dose.

Method.—Preliminary testing was performed with 10 T.U. of old tuberculin intradermally in the left forearm. Of 1,099 children tested, 791 had negative reactions (less than 5 mm. induration), and these children were vaccinated. Vaccination either by the intradermal route or by multiple puncture at a depth of 2 or 3 mm. was performed in strict rotation, the three groups being equally rotated. For the intradermal route the skin in the right deltoid region was cleaned with ether, and 0.1 ml. of vaccine, prepared by adding 1 ml. of sterile water to each ampoule of dried vaccine, was given intradermally. For the multiple-puncture

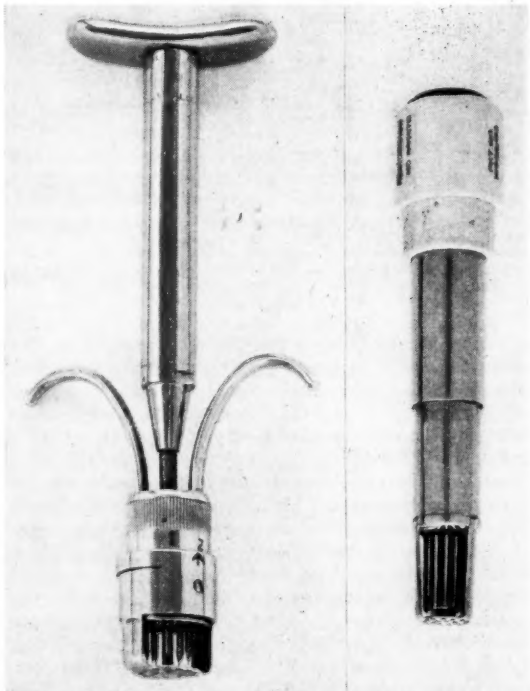

FIG. 1.—Left: Type A gun set to fire 20 needles at a depth of 2 mm. Right: Type B gun set to fire 20 needles at a depth of 2 mm.

method Type A guns fitted with 20 needles which were individually replaceable and which could be adjusted to fire to a depth of 2 or 3 mm. were used (Figs. 1 and 2). The guns were sterilized before each vaccinating session by boiling or autoclaving. The skin over the right deltoid was cleaned with ether, and a drop of vaccine, prepared by adding 0.3 ml. of sterile water to each ampoule containing 25 mg. of B.C.G., was placed on the skin. This was spread by the base-plate of the gun, which was then held firmly on to the arm, the needles being fired to the required depth. The base-plate and needle-tips were then immersed in a solution of equal parts of methylated ether and surgical spirit for 30 seconds. The vaccination sites were inspected six weeks after vaccination and another tuberculin test with 10 T.U. of O.T. was performed. This was read 72 hours later. One year later tuberculin tests with 10 T.U. of O.T. were repeated. The results of these investigations are set out in Table I.

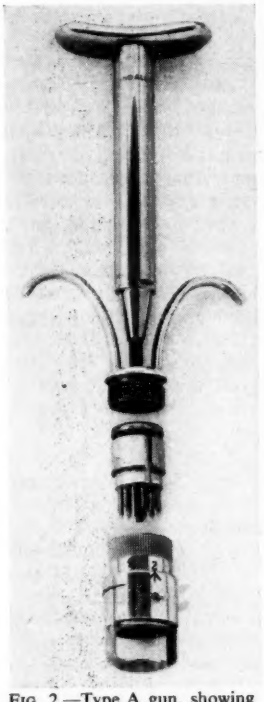

FIG. 2.—Type A gun, showing method of changing needles.

The results of Mantoux-testing have been recorded both as the percentage of positive reactors (5 mm. or more induration) and the mean diameter of induration (including the negative reactors). When the percentage conversion reached 95% or more, minor variations became insignificant, and it then became necessary to rely on the mean induration to give an indication of differences caused by the various factors investigated.

From the first trial (Table I) the following points became obvious: (*a*) there was a marked variation between the results produced by the four investigators taking part in the trial; (*b*) in all four instances the intradermal technique produced greater conversion than the multiple puncture; and (*c*) in none was there any significant difference between the effects of multiple puncture at a depth of 2 mm. compared with a depth of 3 mm.

TABLE I.—*First Trial (School Year 1958–9). Results of 10 T.U. at 6 Weeks and 1 Year. Comparison of Multiple-puncture with Intradermal Vaccination*

Method	Results to 10 T.U.							
	Dr. A		Dr. B		Dr. C		Dr. D	
	Mean Diam. (mm.)	% Pos.	Mean Diam. (mm.)	% Pos.	Mean Diam. (mm.)	% Pos.	Mean Diam. (mm.)	% Pos.
6 Weeks								
Intradermal ..	20·7	100	13·0	99	10·1	94	8·9	100
Multiple puncture, 20/2 mm.	18·8	100	9·6	90	7·7	83	7·0	88
Multiple puncture, 20/3 mm.	18·5	100	9·6	91	8·2	92	8·2	93
1 Year								
Intradermal ..	21·7	100	10·7	84	Not tested			
Multiple puncture, 20/2 mm.	20·1	94	5·2	51				
Multiple puncture, 20/3 mm.	20·2	100	5·0	44				

Second Trial (School Year 1959–60)

It was decided that results of multiple-puncture vaccination were promising enough to make it worth while to try to investigate the factors affecting the efficacy of this method. As the first trial had demonstrated the effect of operator variation, a specific problem was assigned to each worker. By eliminating the variable of operator technique in each group it was possible to study several different problems concurrently.

During this period 2,422 children were tested, and 1,744 children with negative reactions to 10 T.U. were vaccinated. The following factors were assessed: (*a*) the effect of heat on the vaccine; (*b*) differences in concentration of vaccine; (*c*) the effect of roughened needles fitted to the guns; (*d*) comparison of Type A and Type B guns and effect of variation of pressure; and (*e*) correlation of intensity of local reaction and tuberculin sensitivity.

TABLE II.—*Individual Variations in Multiple-puncture Technique*

Operator	Series I. First Trial — 10 T.U. at 6 Weeks			Series II. Second Trial — 10 T.U. at 6 Weeks		
	No. of Cases (2 and 3 mm. Depth Combined)	Mean Induration (mm.)	% Positive	No. of Cases	Mean Induration (mm.)	% Positive
Dr. A	83	18·7	100	A.367 (heat effect)	14·6	97
				B.389	18·4	98
Dr. B	161	9·6	91	A.360 (heat effect)	8·4	74
				B.297	12·8	95
Dr. C	414	8·0	87	213	9·1	99
Dr. D	133	7·8	91	118	9·1	94
Total	791			1,744		

The overall results are shown in Table II. As was to be expected the individual variations were still in evidence, but the degree of conversion six weeks after vaccination in most cases was 95%; in some cases where it was below this figure a reason for this could be found. These individual factors are discussed.

(a) Effect of Heat on Vaccine.—In the first trial the Type A guns were sterilized between sessions by boiling or autoclaving and between individual vaccinations by immersion of base-plate and needle-tips in a mixture of ether 25%, ethyl alcohol 50%, and water 25% for 30 seconds. A question was then raised regarding the efficacy of this method of sterilization, and the gun was therefore flamed after 10 firings in addition to the other methods of sterilization used. It was immediately noticed that the results obtained in this second series of tests fell far below those produced in the preliminary trial. Accordingly more guns were obtained and each operator used four guns, flaming them after every 10 cases as before, but allowing a much longer period of cooling for each gun. An improvement in results was immediately noticeable (see Table III).

(b) Concentration of Vaccine.—Concentrations of 83 mg./ml. and 125 mg./ml. were prepared by adding 0.3 or 0.2 ml. of sterile water to the dried mass (25 mg.) of vaccine in each ampoule. These were used by Dr. B in alternate cases, using different guns for each concentration. The results of this are shown in Table IV and compared with results from Dr. A in two separate

series (one in the first trial and one in the second), using similar concentrations. No difference could be noted in the tuberculin conversion produced by these two concentrations.

(c) *Use of Rough Needles.*—As it had been suggested that roughening of needles might improve the results of multiple-puncture vaccination it was decided to investigate this factor. Needles were roughened either by grinding a screw thread at the tips or by tipping with tungsten. There was no difference in the tuberculin conversion produced by different types of needles.

(d) *Type of Gun and Pressure Used.*—(1) For this series Dr. A used two types of gun both firing 20 needles to a depth of 2 mm. Type A, in which the needles were individually replaceable, was hand-fired by the operator; and Type B, in which the needles were not replaceable, was so adjusted that it fired only when a certain pressure was exerted, as described by Carpenter and Stewart (1959) (see Figs. 1 and 2). The pressure exerted on firing the gun was investigated by firing 10 times into a cork on a spring balance, and it was found that the pressures were reasonably consistent, varying between 7 and 9 lb. (3.2 and 4 kg.). The tuberculin sensitivity produced by the two guns showed no significant difference, suggesting that the pressure of firing was sufficient to drive all the needles to the requisite depth. (2) Dr. C used Type A guns, deliberately firing alternately heavily and lightly. The pressure exerted in this way was investigated as before with a cork on a spring balance. The light pressure was approximately 5 lb. (2.3 kg.) and the heavy pressure varied between 7 and 9 lb. (3.2 and 4 kg.). There was no significant difference in the tuberculin sensitivity produced. These results suggest that a pressure between 5 and 9 lb. (2.3 and 4 kg.) was adequate to fire 20 needles 2 mm. into the skin.

(e) *Correlation between Local Reaction and Mantoux Sensitivity Produced.* — On examining the vaccination records of the children it was obvious that in addition to differences in tuberculin sensitivity there was a good deal of variation in the local lesion produced by various

TABLE III.—*Second Trial. Effect of Heat on Vaccine*

Method of Sterilization	Dr. A		Dr. B	
	10 T.U. at 6 Weeks		10 T.U. at 6 Weeks	
	Mean Induration (mm.)	% Positive	Mean Induration (mm.)	% Positive
Boiling or autoclaving before sessions. Spirit/ether mixture between cases. No heat	18·8	100	9·6	90
Boiling or autoclaving before sessions. Spirit/ether mixture between cases. Heat every 10th case	14·9	96	8·4	74
Boiling or autoclaving before sessions. Spirit/ether mixture between cases. Gun cooled after heating	18·2	98	12·8	95

TABLE IV.—*Effect of Variation in Concentration of Vaccine*

Concentration (mg./ml.)	Dr. A		Dr. B	
	10 T.U. at 6 Weeks		10 T.U. at 6 Weeks	
	Induration (mm.)	% Positive	Induration (mm.)	% Positive
	First trial		Second trial	
83	18·8	100	12·5	95
	Second trial		Second trial	
125	18·2	98	13·0	95

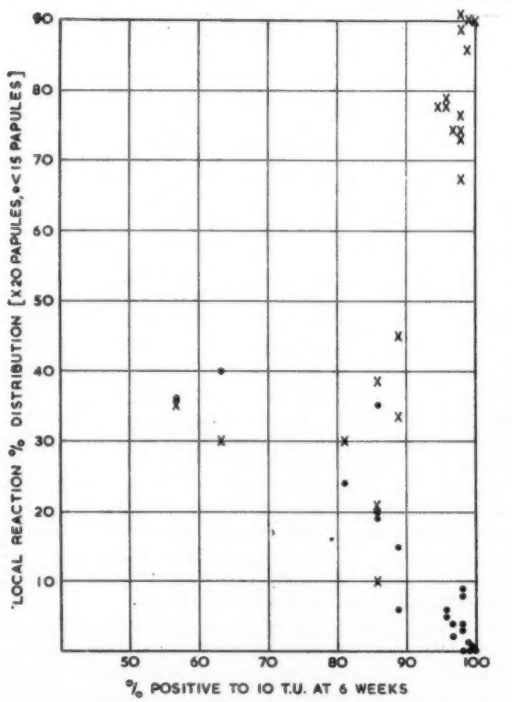

FIG. 3.—Correlation of number of papules in local reaction with result of Mantoux 10 T.U. at 6 weeks. (Drs. A, B, and C.)

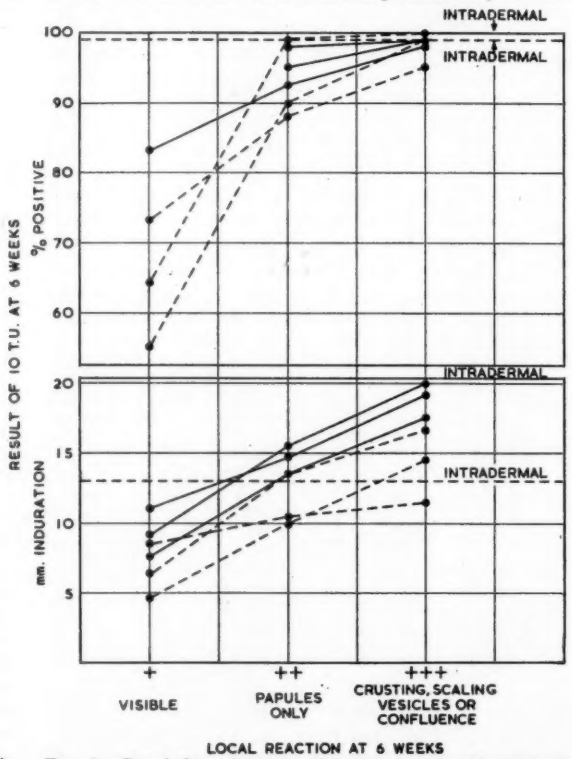

FIG. 4.—Correlation of degree of local reaction with result of tuberculin at 6 weeks. ×——×= Dr. A. ×---×=Dr. B.

operators. The local tissue reaction to B.C.G. vaccination by multiple puncture varies in degree and in the number of papules produced. The number of papules produced in relation to the number of punctures administered may indicate the degree of accuracy of the vaccinator. In order to see if this was the case the percentage conversion to 10 T.U. at six weeks was plotted against the percentage of cases in which 20 papules were produced and the percentage of cases in which fewer than 15 papules were produced by a 20-needle gun (Fig. 3). The factors influencing the number of papules produced may be the technique of the vaccinator, defects in the gun, or variations in the vaccine. The fact that 20 papules are produced indicates adequate spreading of the vaccine, even application of the gun by the vaccinator, and reasonable condition of the gun. If a few needles are blunted or shortened there will be occasional papules missing. If, however, there are a large number of papules missing this suggests either inadequate spreading of the vaccine or uneven application of the gun and is likely to be related to the operator technique. It is notable that when Dr. B (whose results showed the greatest variability) produced a high percentage of reactions with 20 papules the Mantoux conversion was adequate, whereas there was poor Mantoux conversion in those series in which a higher percentage of reactions of fewer than 15 papules were produced. As the same guns and vaccine were used throughout, it is suggested that the variations were in the technique. With regard to the degree of reaction there is likely to be more individual variation in the readings, but it is possible to compare the percentage positive and the mean induration to 10 T.U. at six weeks with the degree of reaction from individual vaccinators. In all cases a degree of reaction producing pustules, scaling, or confluence was associated with tuberculin conversion equivalent to that produced by intradermal vaccination (see Fig. 4). It is therefore apparent that successful technique in vaccination is extremely important.

Discussion

Although multiple-puncture B.C.G. vaccination is by no means a new method of administration and has been used by Birkhaug (1944) since 1939 and by Rosenthal (1939) since 1937, there is as yet no certain evidence with regard to all the factors necessary to ensure that vaccination by this method should be as effective as possible. In all previous reports (Forssman, 1946; Hertzberg, 1948; Geser, 1954; Griffith, 1959; Rosenthal, 1960) in which multiple-puncture vaccination has been compared with intradermal in groups of children of school age, it has been found that multiple-puncture vaccination is less effective than intradermal. This has also been found to be the case in the present trial. Investigations which will increase the efficiency of multiple-puncture vaccination have not been numerous and certainly more need to be undertaken. Although multiple-puncture vaccination would appear to be a simple and easy method of B.C.G. vaccination it is evident that there is considerable variation between the results of individual operators, and that the technique of this method will need to be carefully considered and assessed and be adhered to very strictly. There is no doubt that the children concerned prefer to be inoculated by the multiple-puncture method, and this may have an effect on the acceptance rate and thus the total number of protected children.

It is likely that a certain minimal concentration of vaccine is necessary. It is possible that the concentration of 20 mg./ml. favoured by Forssman (1946) and Geser (1954) was inadequate, and that the concentrations used in this present trial of 83 mg./ml. and 125 mg./ml. produced no appreciable difference in clinical efficacy because both concentrations were above the margin required for maximal effect. Griffith (1959), using the same freeze-dried vaccine as in the present trial, reports successful results with a suspension of 50 mg./ml.; Hopper (1960) found a concentration of 1.8 mg./ml. to be quite inadequate. It is probable that eventually the concentration may need to be measured by the number of viable organisms per ml.

Rosenthal (1957) stated that increasing the number of punctures increases the efficiency of vaccination, and Griffith (1959) suggested that the number of punctures used in schoolchildren should be 40. As the guns in the present trial were fitted with only 20 needles it was decided to use this number of punctures in assessing some of the other factors. In further investigations it may well be advisable to increase the number of punctures to 40. It has been observed in the newborn that an increased number of punctures is effective in prolonging the efficiency of vaccination (Griffiths, 1960).

The importance of the effect of heat on the B.C.G. vaccine has not been previously reported, possibly because heat sterilization is not necessary with Rosenthal's (1957) technique, and is not advocated by Birkhaug (1947). In the present series there was no doubt about the deleterious effect of using a hot gun, and it is possible that this may have been one of the factors causing the discrepancy in results reported from Cardiff and Pembrokeshire by Griffith (1959).

It is also probable that the type of gun used may affect the results. No difference has been noted in the effects produced by 20-needle guns Type A and Type B, but it is possible that further investigations will lead to modifications in the guns to produce improved results.

Hopper (1960) reported that as the needles became blunter through the effects of flaming and clogging with carbon deposits, the clinical results deteriorated. We have found no differences in results using specially roughened needles.

The fact that there was evidence of considerable variation between operators emphasizes the necessity for establishing a reliable technique in the use of multiple-puncture instruments, to ensure adequate penetration of all the needle points.

Summary

2,535 Cheshire schoolchildren were vaccinated with the British freeze-dried B.C.G. by the multiple-puncture technique between February, 1959, and June, 1960.

Multiple-puncture vaccination with freeze-dried B.C.G. was less effective than intradermal vaccination with a less concentrated freeze-dried vaccine.

When guns firing 20 needles at a pressure of 5–9 lb. (2.3 and 4 kg.) were used, there was no significant difference in the clinical effects produced by puncturing to depths of 2 or 3 mm., using vaccine concentrations of 83 mg./ml. or 125 mg./ml., self-firing or operator-fired guns, and rough or smooth needles.

It was found that heat had a deleterious effect on the vaccine, and adequate time for cooling was necessary if this method of sterilization was practised.

Although this is apparently a simple method there was a great deal of operator variation, and further investigations into the technical factors affecting the results of multiple-puncture vaccination need to be carried out in the hope of modifying this technique to make the results comparable with those produced by intradermal vaccination.

We thank Dr. Arnold Brown, Medical Officer of Health for Cheshire County Council, for allowing this work to be carried out, and Professor Wilfrid Gaisford, Department of Child Health, Manchester University, for his encouragement and advice. The vaccine was prepared at, and supplied by, the Glaxo Laboratories, and we are grateful to Dr. J. Ungar and Dr. P. W. Muggleton for their practical help throughout the investigation. The Type A guns and the roughened needles were supplied by Messrs. Allen and Hanburys, of London, and the Type B self-firing gun was supplied for the B.T.A. pilot trial by Messrs. H. G. East, of Oxford. The photographs were taken by Mr. D. F. Boxall.

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MEGALOBLASTIC ANAEMIA ALTERNATING WITH POLYCYTHAEMIA VERA

BY

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The development of polycythaemia vera in a patient previously proved to have megaloblastic anaemia associated with vitamin-B_{12} deficiency is a haematological rarity, and only a small number of such cases, varying in degree of detailed study, have been reported. It is of interest to note that Sir William Osler (1903) in his classical paper on polycythaemia mentions a patient who was "as red as a beet" and suspected of having polycythaemia vera, but who had had, in fact, blood-count changes resembling pernicious anaemia. The most recent accounts of the association of pernicious anaemia and polycythaemia vera in the same patient are those of Hinz (1957) and Ellman and Bowdler (1958). Zarafonetis *et al.* (1957) describe the unique sequence of pernicious anaemia, polycythaemia, and acute leukaemia occurring in the same patient.

Case Report

A married woman aged 66 was first seen by one of us (W. R.) in October, 1945. She complained of loss of weight, lethargy, and cramps in the legs. These symptoms had developed gradually over the preceding few months and her memory had deteriorated. Her previous health had been good, her husband stating that she had usually been of good facial colour.

Clinically she was a small, spare woman with slight kyphosis. She did not appear obviously anaemic. No noteworthy physical signs of disease were found apart from a sensation of fullness on palpation of the left hypochondrium. When seen in consultation by Dr. Bellingham Smith a diagnosis of carcinoma of the stomach or colon was considered. Blood examination at that time showed: Hb, 36% (5.3 g./100 ml.), R.B.C., 2,110.000/c.mm.; C.I. 0.9. The red cells showed macrocytosis, and varied in size and shape. A barium-meal examination showed no radiological abnormality of stomach or duodenum, but as the patient was unwilling to be admitted to hospital (an attitude she firmly maintained subsequently) she was treated at home with intramuscular injections of liver extract ("campolon") and oral iron. Such treatment was associated with rapid clinical and haematological improvement (see Chart) and five months later the somewhat surprising result of Hb 135% (20 g./100 ml.) and R.B.C. 7,280,000/c.mm. was reported. Clinically she had become obviously polycythaemic with red face and watering blood-shot eyes. A mass now readily palpable in the left hypochondrium was regarded as an enlarged spleen with a firm edge. The patient had lost all her old symptoms and felt remarkably well.

All treatment was discontinued and she apparently remained well until the autumn of 1948, when her original symptoms returned. In December, 1948, severe macrocytic anaemia was again present: Hb, 44% (6.5 g./100 ml.); R.B.C., 2,000.000/ c.mm.; C.I., 1.1. The spleen was larger. Treatment with further parenteral liver extract alone was again followed by prompt improvement with another meteoric rise in Hb and red-cell count. Within three months of restarting liver therapy the Hb was 140% (20.8 g./100 ml.) and R.B.C. 8,500.000/c.mm. She felt well but was very plethoric. The spleen was now palpable fully a handbreadth below the left costal margin, and the liver was also palpable. There had never been any enlargement of lymphatic glands —or symptoms of glossitis, although her tongue was very red. Once again treatment was stopped, but anaemia returned. Liver extracts of various sources of manufacture were subsequently given intermittently.

In March, 1951, the patient was referred to one of us (J. N. M. C.) at St. George's Hospital, London, and more detailed studies were made. She was then aged 72 and had received an injection of refined liver extract a month before her attendance at hospital.

Clinically she did not appear anaemic—her face being somewhat florid, her conjunctivae injected, and her tongue very red although it was not smooth. While she was of small build there were no signs of wasting and there was no evidence of enlargement of superficial lymphatic glands. The abdomen was protuberant; the spleen was palpable fully a handbreadth below the left costal margin and the liver was also palpably enlarged. There was no evidence of ascites. Tachycardia associated with a collapsing pulse was present; B.P. 185/85 mm. Hg. There was no abnormality of the reflexes. Vibration sense over the shins was poorly appreciated. The urine was normal on routine testing; *X*-ray examination of the chest, spine, and long bones showed no abnormality apart from senile osteoporosis and osteoarthritis. A radiograph of the chest showed the lung fields to be clear, the transverse diameter of the heart being increased.

Blood examination showed macrocytic anaemia: Hb, 52% (7.7 g./100 ml); R.B.C., 1,830,000/c.mm.; P.C.V., 23%; M.C.V., 126 cubic microns; M.C.H.C., 33%; W.B.C., 10,700/c.mm. (polymorphs, many showing nuclear hypersegmentation, 76%, lymphocytes 19%, monocytes 5%). Red cells showed considerable variation in shape and size, with many macrocytes and rather oval cells. Platelets were numerous, with many large forms. Serum bilirubin was 1.3 mg./100 ml., serum urea 28 mg./100 ml., and direct Coombs test and Wassermann reaction were negative. Sternal puncture was easily performed, but only a small and unsatisfactory specimen of marrow was obtained. Smears showed megaloblasts, transitional cells, and large myelocytes and metamyelocytes—but such nucleated cells were not numerous. Masses of platelets were present but few intact megakaryocytes.

40 μg. of vitamin B_{12} was given intramuscularly. In 17 days the Hb had risen to 89% (13.2 g./100 ml.), R.B.C. to 3,800,000/c.mm., and P.C.V. to 41%. A neutrophil leucocytosis of 23,000/c.mm. (metamyelocytes 17%, polymorphs 67%, eosinophils 4%, lymphocytes 11%, monocytes 1%) had occurred. E.S.R. (Wintrobe) was 2 mm. in one hour. There was associated clinical improvement. After a further single injection of 20 μg. of vitamin B_{12} the Hb rose to 109% (16.1 g./100 ml.), the R.B.C. to 4,900,000/c.mm., P.C.V. 52%. A neutrophil leucocytosis of 18,000/c.mm. persisted: occasional myelocytes were found, but no cells more primitive than this.

Even with intramuscular doses of vitamin B_{12} as small as 20 μg. every three weeks, the patient had become polycythaemic again when tested two months later (see Table and Chart). A test meal at this stage—which upset the patient and caused collapse—showed histamine-fast achlorhydria; Hb was 118% (17.6 g./100 ml.), R.B.C. 7,250,000/c.mm., P.C.V. 63%. Macrocytosis had disappeared (M.C.V. 86 cubic microns) and the red cells were now hypochromic (M.C.H.C., 27.5%). White cells remained elevated at 23,600/c.mm., with 6% metamyelocytes and increase in polymorphs. Nuclear hypersegmentation of these latter cells had virtually disappeared. Platelets numbered 440,000/c.mm.

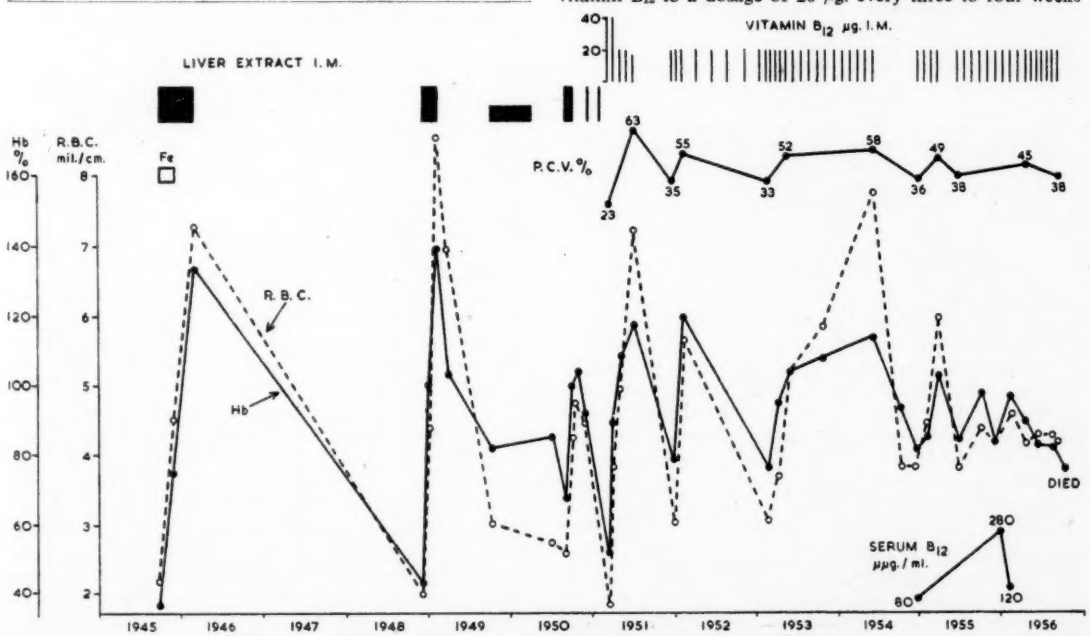
Initial Therapy with Intramuscular Vitamin B_{12} in 1951

	Before Therapy	After 140 μg. Vitamin B_{12} I.M. Spread Over 3 Months	After Blank Injections Over 5 Months
Hb ..	52% (7·7 g./100 ml.)	118% (17·6 g./100 ml.)	78% (11·4 g./100 ml.)
R.B.C. ..	1,830,000/c.mm.	7,250,000/c.mm.	3,080,000/c.mm.
P.C.V. ..	23%	63%	35%
M.C.V. ..	126 μ^3	86 μ^3	113 μ^3
W.B.C. ..	10,700/c.mm. occasional metamyelocytes	23,600/c.mm. some myelocytes and more frequent metamyelocytes	11,800/c.mm. occasional metamyelocytes
Platelets ..	Numerous	440,000/c.mm.	350,000/c.mm.

The patient was now feeling well, although she remained hypertensive and was rather light-headed at times. As she had faith in the injections which were being given to her, placebo injections of sterile saline were given as from July, 1951. As shown in the Chart, there was a fall in Hb, R.B.C., P.C.V., over the subsequent five months. Macrocytosis returned (M.C.V. 113 cubic microns), the leucocyte count was then 11,800/c.mm., and once again nuclear hypersegmentation of the polymorphs was obvious. Platelets were 350,000/c.mm. Reticulocytes, independent of therapy for five months, were 6%; bilirubin 0.75 mg./100 ml. and serum uric acid 5.3 mg./100 ml. Empirical liver-function tests were not noteworthy.

Three injections of 20 μg. of vitamin B_{12} at fortnightly intervals were again followed by polycythaemia (P.C.V. 55%) and a leucocytosis of 25,000/c.mm. (myelocytes 2%, metamyelocytes 11%, polymorphs 68%, eosinophils 6%, lymphocytes 10%, monocytes 3%). Reduction of dosage of vitamin B_{12} to 20 μg. every six weeks was insufficient to keep her Hb and P.C.V. within normal range and the leucocyte count fell to 11,000/c.mm. Injections of 20 μg. every month, however, kept values in fair balance between polycythaemia and anaemia during 1953, but on the same dose she became polycythaemic once again in June, 1954. She was becoming more uncomfortable owing to the greatly enlarged spleen extending into the pelvis. The liver was palpable 2 in. (5 cm.) below the right costal margin. All treatment was stopped for six months, and at the end of this time a repeat bone-marrow examination showed megaloblastic change—although once again there was difficulty in obtaining the specimen. A serum vitamin-B_{12} estimation by the *Euglena gracilis* technique gave a result of 80 $\mu\mu$g./ml.

As shown in the Chart, adjustment of intramuscular vitamin B_{12} to a dosage of 20 μg. every three to four weeks



Haematological data relative to liver and vitamin-B_{12} therapy over 11 years.

kept the Hb, red cells, and P.C.V. at a reasonable level during 1955 and 1956. Clinically, the gross splenomegaly rendered life most uncomfortable and she developed rectal prolapse, which was treated conservatively. During this time repeated leucocyte counts ranged from 15,000 to 20,000/c.mm. with polymorph increase—occasional myelocytes, metamyelocytes, and, rarely, normoblasts being found in blood films, but no white cells of more primitive type. The platelet count was 269,000/c.mm. She developed congestive cardiac failure, and treatment with mersalyl was given. The patient's condition deteriorated and she died on September 22, 1956.

Post-mortem Findings

Necropsy, four hours after death, was carried out by Dr. W. S. Killpack at Ealing. The body was wasted and showed oedema of the legs. The heart was dilated and the muscle showed brown atrophy. The right ventricle was hypertrophied. Coronary arteries and valves were healthy and there was little aortic atheroma. There were small effusions in both pleural sacs. The lungs were bulky and oedematous, the cut lower lobes being firm and brown, suggesting haemosiderosis.

Mouth, tongue, oesophagus, stomach, and intestines appeared healthy. No specimen of stomach was obtained from histology.

The liver, enlarged and firm, weighed 2,500 g., the cut surface being dark red. Gall-bladder and pancreas appeared healthy. The spleen was grossly enlarged and weighed 1,360 g. There were no splenic adhesions or infarcts. The cut surface was firm and dark red. The para-aortic lymph nodes showed slight enlargement. The bone-marrow of sternum and lumbar vertebrae was dark red and semi-diffluent. A long bone was not examined. No abnormality was found in brain meninges, suprarenals, or thyroid.

Histology.—Sections of the lungs showed evidence of bronchopneumonia with haemosiderin-laden macrophages in the alveolar spaces. Kidney sections showed signs of early glomerulonephritis. The liver showed a periportal exudate of lymphocytes but no other abnormality, apart from iron pigment in the Kupffer cells. Spleen sections showed evidence of autolysis and a small amount of iron pigment was found. On prolonged search an occasional cell resembling a megakaryocyte cound be found but no evidence of extramedullary haemopoiesis. Malpighian bodies were more widely spaced than normal, but showed no structural abnormality. Sections of the sternal and vertebral bone-marrow showed a general marked hyperplasia with numerous prominent megakaryocytes and abundant normoblasts and granulocytes. Reticulin was present in moderate amounts. No recognizable megaloblasts could be found. Sections of the abdominal lymphatic glands showed nothing of pathological significance. Death was attributed to pulmonary oedema associated with polycythaemia vera.

Discussion

Red-cell counts above the normal range after liver therapy for pernicious anaemia were noted on occasion by Minot and Murphy (1926) and are also referred to by Koessler and Maurer (1927). However, as is stated by Ellman and Bowdler (1958), this appears only rarely as a mild non-progressive erythrocytosis, and it is widely held that generous doses of liver or vitamin B_{12} do not raise blood-count values of normal subjects or patients with pernicious anaemia above physiological limits. Exceptionally, as occurred in our patient, vitamin-B_{12} deficiency may develop in an individual with a propensity towards myeloproliferative disease, but the number of reported instances of this combination of blood disorders is small. The occurrence of polycythaemia vera and pernicious anaemia in the same patient has been reported by Birnie (1936), Ferrary (1942), Galt *et al.* (1952), Skouby (1952), Hinz (1957), and Ellman and Bowdler (1958). Other likely instances of this phenomenon are reported by Avery (1930) and by Emile Weil and Boic (1932). The case described by Zarafonetis *et al.* (1957) showed the sequence of pernicious anaemia, polycythaemia, and acute myeloblastic leukaemia; and Baikie *et al.* (1958) report a case of pernicious anaemia, in which polycythaemia, leucocytosis, and thrombocythaemia developed after treatment with vitamin B_{12}—the platelet count rising to 1,750,000/c.mm. Wellington and Whitcomb (1960) describe a similar case. Croft (1956) studied a remarkable case in which myelosclerosis, polycythaemia, myeloid leukaemia, and vitamin-B_{12} deficiency were all demonstrated at various times over a period of 13 years. Thus it is apparent that on rare occasions patients prone to a myeloproliferative syndrome may also develop vitamin-B_{12} deficiency. The myeloproliferation may show emphasis on red-cell production or on granulocytes, platelets, or fibroblasts, and the degrees of such vary from time to time. It is masked or modified should there be a deficiency of vitamin B_{12}. Cases of uncomplicated polycythaemia vera show a normal or high serum vitamin-B_{12} value (Mollin and Ross, 1955), and instances of myelosclerosis being associated with a rapid folic-acid clearance test have been reported by Chanarin *et al.* (1958). However, we know of no instance of a case of polycythaemia vera being complicated by megaloblastic anaemia proved to be due to folic-acid deficiency.

In the past it has been suggested that polycythaemia vera was the antithesis of pernicious anaemia and that this condition was due to an excessive secretion of gastric haemopoietic factor (see Wintrobe, 1956). However, the occurrence of both diseases in the one patient renders this an untenable concept; in the case reported by Ellman and Bowdler (1958) it was proved that added intrinsic factor was needed to increase absorption of orally administered radioactive vitamin B_{12}. As our patient was unwilling to be admitted to hospital it was impossible to use this technique or to carry out fat-balance studies. There was no obvious clinical evidence to suggest steatorrhoea; the serum vitamin-B_{12} value was low after a period of no therapy: there was histamine-fast achlorhydria; and the haematological response to small doses of parenteral vitamin B_{12} was dramatic. A diagnosis of pernicious anaemia developing into polycythaemia vera when treated with either liver or vitamin B_{12} would appear almost indisputable, and this occurrence a coincidence. In 1951, in spite of recent injections of refined liver extract, megaloblastic anaemia was present, but the patient promptly showed haematological improvement with small intramuscular doses of vitamin B_{12}. It must be concluded that the batch of refined liver extract used at that time must have contained very little vitamin B_{12} (see Adams and Timbury, 1959).

As was observed in several of the other cases which have been reported, our patient usually showed a higher granulocyte count and relatively higher platelet count values when treated with liver or vitamin B_{12} than when in the stage of megaloblastic anaemia. In all reported cases splenomegaly has been a feature, although this was not always noted when the patients were first seen. Most cases have presented in the first place in an anaemic phase—polycythaemia developing subsequently. Wellington and Whitcomb (1960), however, reported the case of a patient with poly-

cythaemia vera who, after venesections, developed an anaemia resembling pernicious anaemia and who responded dramatically to liver therapy.

Wellington and Whitcomb (1960), however, reported the case of a patient with polycythaemia vera who, after venesections, developed an anaemia resembling pernicious anaemia and who responded dramatically to liver therapy. This patient died from pyelonephritis following prostatectomy. At necropsy normal red-blood-cell maturation was found in the bone marrow, as was myeloid metaplasia in the spleen. The case reported by Hinz (1957) showed cerebral haemorrhage and necrosis at necropsy, but otherwise the post-mortem findings were generally similar to those in the case we have described.

Summary

A case is described of a woman showing megaloblastic anaemia, who developed features of polycythaemia vera after treatment with liver or vitamin B_{12}. Anaemia recurred on discontinuation of treatment.

Clinical and haematological data over a period of 11 years are recorded. The patient was ultimately kept in satisfactory haematological balance with infrequent small doses of parenteral vitamin B_{12}.

The necropsy findings are summarized.

The occurrence of vitamin-B_{12} deficiency developing in a patient prone to myeloproliferative disorder is regarded as a coincidence.

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Ageing, its Changes and its Promise is the report of the Tenth National Conference on the Care of the Elderly which was held in Blackpool in the spring of 1960. The conference covered the housing of the elderly; social policies; residential care for the physically and mentally frail; development in hospital care and hospital services; and a forward view of the next two years. There were discussion groups on visiting; clubs; preparation for retirement; training and recruitment; housing; and day centres and workshops. The report costs 5s. from the National Old People's Welfare Council, 26 Bedford Square, London W.C.1.

MEGALOBLASTIC ANAEMIA IN CONGENITAL SPHEROCYTOSIS

BY

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The purpose of this paper is to report two cases of congenital spherocytic haemolytic anaemia complicated by megaloblastic anaemia. The first case occurred in association with pregnancy. So far as we are aware, the second is unique in that, apart from the congenital spherocytosis, no cause for megaloblastic erythropoiesis could be discovered.

Case 1

The patient became pregnant at the age of 28 while in Germany. She first attended the antenatal clinic when 16 weeks pregnant and was found to have a haemoglobin level of 11.4 g./100 ml. At 22 weeks she began to complain of breathlessness and swelling of the ankles, and was noted to have a definite yellow tint to her skin. The dietary history was satisfactory and there was no abnormality of bowel habit.

She was admitted for investigation and the blood count showed: haemoglobin, 6.5 g./100 ml.; red cells, 1,790,000/c.mm.; white cells, 7,200/c.mm.; packed cell volume, 18%; mean corpuscular haemoglobin concentration, 36%; mean corpuscular volume, 101 cubic microns; reticulocytes, 7%. The red blood cells showed anisocytosis and macrocytosis with some polychromasia and an occasional normoblast. Some of the polymorph leucocytes were noted to be hypersegmented, but the platelets were normal. The bone-marrow showed erythroid hyperplasia and erythropoiesis was megaloblastic; leucopoiesis was normal. Free acid was present in the stomach. The serum bilirubin level was 1 mg./100 ml.

A diagnosis of megaloblastic anaemia of pregnancy was made and the patient was treated with folic acid in a dose of 10 mg. a day. A reticulocyte peak of 20% was reached on about the eighth day, but the haemoglobin level and red-cell count showed little change, and 19 days after her admission the haemoglobin was still 6.2 g./100 ml., and the red-cell count 1,420,000/c.mm. She was transfused with 3 pints (1.7 l.) of compatible blood, which raised her haemoglobin level to 9 g./100 ml. Despite continued folic acid therapy the haemoglobin level six weeks later had fallen to 6.5 g./100 ml. She was transfused with a further 4 pints (2.3 l.) of packed cells and three weeks later was delivered of a baby girl. Her haemoglobin level at this time was 10.4 g./100 ml. After the puerperium folic acid therapy was stopped, and five months after the delivery her haemoglobin level was 11.8 g./100 ml., red-cell count 4,770,000/c.mm., colour index 0.83, and white-cell count 9,200/c.mm.

Second Pregnancy.—The patient returned to this country and reported to the Haematology Clinic of the Royal Infirmary, Edinburgh, in the 14th week of her second pregnancy. She was complaining of severe lethargy, but was otherwise well and physical examination was negative.

Investigations.—The blood counts were as follows: haemoglobin, 9.9 g./100 ml.; red-cell count, 3,630,000/c.mm.; colour index, 0.92; white-cell count, 5,800/c.mm. The blood film showed some anisocytosis of the red blood cells, with the presence of both macrocytes and microspherocytes. The serum vitamin B_{12} level was 80 $\mu\mu$g./100

ml. (*Lactobacillus leichmannii* method without the addition of cyanide. Normal range, 110 to 810 μμg./100 ml. according to Girdwood, 1960).

Treatment.—Folic acid in a dose of 15 mg. daily was given by mouth and continued until the end of the puerperium.

Progress

Two months after starting folic-acid therapy the haemoglobin level was 9.8 g./100 ml., red blood count 3,230,000/c.mm., colour index 1.0, and reticulocyte count still 5.5%; two months later her haemoglobin level was 12 g./100 ml., red blood count 4,350,000/c.mm., colour index 0.93, and reticulocytes 7.7%. There was a slight excess of urobilinogen in the urine. Both the direct and the indirect Coombs test were negative and there was no evidence of any specific blood-group antibodies. On November 17, 1959, the patient was delivered of a live male child who was free of anaemia.

A red-cell survival test carried out by means of labelling the patient's own cells with radioactive chromium five months after delivery showed significant shortening of the red-cell survival time, the half-life of radioactivity in the patient's blood being 19 days (normal, 25–32 days). The reticulocyte count at this time was 3.4%, but there were no significant numbers of microspherocytes in the patient's blood nor in the blood of her two children and her mother.

Comment.—A case of haemolytic anaemia probably due to mild congenital spherocytosis presenting with megaloblastic anaemia in her first pregnancy. Folic acid was begun early in the second pregnancy, which was uneventful.

Case 2

This patient, a man aged 43, was perfectly well until one month before he was seen as an out-patient. He then developed a febrile illness, with generalized muscular pains and frontal headaches. The fever subsided, but he remained weak and lethargic. There was no previous history of jaundice.

Splenectomy had been performed on his brother in 1949 and on his sister in 1957 for congenital spherocytosis. All five of the sister's children have spherocytosis. The patient's father was considered for splenectomy in 1926 during an illness characterized by anaemia and jaundice, but he died at the age of 73, the operation not having been performed.

On examination the skin and mucous membranes were pale and there was an icteric tinge in the sclerae. The tip of the spleen was just palpable at the left costal margin.

Investigations.—Haemoglobin level, 6.7 g./100 ml.; red-cell count, 2,000,000/c.mm.; colour index, 1.12; white-cell count, 6,400/c.mm.; reticulocytes, 2.2%. The blood film showed the presence of microspherocytes and an occasional polychromatic cell. The serum bilirubin was 1.5 mg./100 ml., and urobilinogen was present in excess in the urine. The direct Coombs test was negative and no platelet antibodies could be detected. The blood urea nitrogen was 19 mg./100 ml.

Progress

The patient was admitted to hospital about one month later, when he was noted to have leucopenia of 800/c.mm. Blood transfusion with 4 pints (2.3 l.) of blood was carried out, and one week later the haemoglobin level was 8.9 g./100 ml. The leucopenia persisted, the white-cell count being 1,000/c.mm. (neutrophils 42%, lymphocytes 43%, monocytes 3%, eosinophils 10%, basophils 2%), and the patient was now found to be thrombocytopenic with only 15,000 platelets/c.mm. The leucopenia gradually improved, rising to a maximum of 3,800/c.mm. after a further week, but the platelet count fluctuated between 15,000 and 83,000/c.mm. The bone-marrow showed normoblastic hyperplasia, but some of the red-cell precursors had undergone megaloblastic change. Myeloid and platelet precursors were normal.

Treatment with folic acid, in a dose of 5 mg. three times a day, was instituted, and after an interval of two days the haemoglobin level was 9.6 g./100 ml., the white-cell count 7,000/c.mm., and platelets 140,000/c.mm

Splenectomy was performed, and during the next few days the platelets rose, reaching a level of 660,000/c.mm. ten days after operation. The white-cell count was maintained at about 4,500/c.mm. Repeat bone-marrow examination showed that the cytology had returned to normal and erythropoiesis was normoblastic. Platelets were abundant.

Post-operative Vitamin B_{12} and Folic Acid Studies

Serum vitamin B_{12} (*L. leichmannii* method with added cyanide)—126 μμg./ml. normal level, 140 to 1,000 μμg./ml.: Girdwood, 1960). Vitamin-B_{12}-absorption test, normal (20% faecal recovery of radio-activity). Folic acid excretion test, normal (the urinary output after a 5-mg. injection of folic acid was 1.95 mg. and the output of 5-mg. oral dose was 2.3 mg. Excretion index, 117.9%) (Girdwood, 1960). Maximal histamine secretion test (Kay, 1953), 0.9 mEq in the post-histamine hour.

Comment.—A case of congenital spherocytosis complicated by pancytopenia and megaloblastic anaemia.

Discussion

Megaloblastic erythropoiesis is occasionally observed when there is a prolonged increase in blood-cell production from a variety of causes—for example, leukaemia, erythraemic myelosis, haemolytic disease. The reason for the appearance of megaloblasts in the marrow in these conditions, while not definitely known, is thought to be due to deficiency of folic acid (Girdwood, 1956). Chanarin *et al.* (1959a) have been able to show that the clearance rate of an injected dose of folic acid from the plasma is increased in patients with haemolytic disorders compared with normal subjects, and this may indicate an increased requirement of folic acid and perhaps of other haemopoietic factors when marrow turnover is accelerated; it follows that a deficiency of these factors in varying degrees of severity could conceivably arise. Although the utilization of iron is also increased in these circumstances, iron falls into a different category because of the substantial body stores of this element and because the iron which is released from haemoglobin katabolism is almost all available for re-use.

Megaloblastic blood formation has been more often observed in association with the haemolytic anaemias than in the myeloproliferative syndrome, but this may merely reflect a tendency to longer survival in the former and hence deficiency of haemopoietic factors. Megaloblastic anaemia has been reported as a complication of acquired haemolytic anaemia (Baikie and Pirrie, 1956; Chanarin *et al.*, 1959a), thalassaemia (Crosby and Sacks, 1949; Goldberg and Schwartz, 1954; Jandl and Greenberg, 1958), and sickle-cell anaemia (Jonsson, 1958). There have also been instances of megaloblastic anaemia as a complication of congenital spherocytosis (Davidson, 1952; Drury and Geoghegan, 1957; Giles and Shuttleworth, 1958; Kohler *et al.*, 1960); however, so far as we are aware, all such cases have been associated with pregnancy.

The fact that pregnancy has often been implicated when haemolytic disease has been complicated by megaloblastic blood formation is worthy of comment. It has been known for some time that pregnancy may lead to an exacerbation of haemolytic anaemia, and McElin *et al.* (1950) think that this is particularly likely to occur from the third month of gestation onwards. Baker *et al.* (1958) showed that the levels of vitamin B_{12} and folic acid were higher in the serum of newborn infants than those found simultaneously in their mothers. Other studies have shown that maternal serum

vitamin-B_{12} levels decline through pregnancy, and after delivery infant levels are approximately twice those of the mother (Okuda *et al.*, 1956; Boger *et al.*, 1957; Dumont, 1957), and the low levels of serum vitamin-B_{12} reported in the case of Kohler *et al.* (1960) and in the case recorded above are interesting in this respect. More recently, observations made in normal subjects indicate that in pregnancy there may often be an increased clearance of intravenously injected folic acid from the blood (Chanarin *et al.*, 1959b; Girdwood and Delamore, 1960).

The first patient described above presented in her first pregnancy with a megaloblastic anaemia that was unresponsive to folic acid therapy and with haemolytic anaemia in the second. It is possible that the prophylactic administration of folic acid in the second pregnancy may have prevented the development of megaloblastic erythropoiesis. Apart from the time of pregnancy the health of this patient has been entirely normal. In addition to this case, we have recently observed two other patients who were similar in that congenital spherocytosis was first suspected in pregnancy because on routine examination of the blood they were found to have anaemia and unusual reticulocytosis. In all of these patients the red-cell defect may well have remained unrecognized except for the advent of pregnancy.

The second patient is unusual in that we have not found records of any others in whom congenital spherocytosis produced megaloblastic anaemia in the absence of some other conditioning factor. Although the patient had a low level of vitamin B_{12} in the serum he had hydrochloric acid in his gastric juice and normal absorption of vitamin B_{12}. He had a sudden crisis after an infection, and his blood picture was later characterized by leucopenia and thrombocytopenia. In the short period available for observation before operation, the administration of folic acid seemed to improve the white-cell and platelet counts.

It would appear that when haemolytic anaemia exists conditioned depletion of folic acid and perhaps also of vitamin B_{12}, as may occur in pregnancy, may aggravate the anaemia and lead to megaloblastic erythropoiesis; and that when a megaloblastic anaemia is discovered in pregnancy with an unusual reticulocytosis and is unresponsive to the usual therapy haemolytic anaemia should be considered. Moreover, as stated by Chanarin *et al.* (1959a), "a sudden increase in severity of anaemia or the onset of reticulocytopenia in a patient who is known to have a long-standing haemolytic anaemia should suggest the possibility that megaloblastic change is developing." We would add that in view of the appearance of leucopenia and thrombocytopenia in Case 2, sudden reduction in the white-cell and platelet counts may also indicate the need for examination of the marrow.

Summary

The cases of two patients in whom congenital spherocytosis is complicated by megaloblastic anaemia are described. In one patient it occurred in association with pregnancy, but in the other there appeared to be no complicating factor. It is suggested that if a patient suffering from chronic haemolytic anaemia suddenly becomes more anaemic, or develops leucopenia or thrombocytopenia, megaloblastic change should be suspected.

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CONGENITAL PYLORIC STENOSIS IN THE AFRICAN INFANT

BY

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In Europe and America congenital pyloric stenosis is regarded as the commonest condition requiring surgical treatment in infancy, and in Britain the incidence of the disease is usually estimated at three or four cases per thousand births. No case of this condition occurring in an African infant had been reported in the English literature until Petcher (1953) described two cases in Northern Nigeria. Since then, further cases have been reported from East, Central, and South Africa (Shepherd-Wilson and Gelfand, 1955; Luder, 1956; Griffiths, 1956; Hamilton, 1957; Menezes and Thethravusamy, 1957; Scragg, 1958; Boroda, 1960). A total of 11 cases of congenital pyloric stenosis affecting African infants have now been described, and their clinical details are summarized in Table I. In addition, Griffiths (1956) mentioned one and Scragg (1958) noted two further cases as having been diagnosed at their hospitals, but the cases were not described.

During the past three years six cases of congenital pyloric stenosis affecting Nigerian infants have been diagnosed and treated surgically in Ibadan, two cases in Lagos, and two cases in Enugu. They are reported briefly in Table II. In all these cases the typical pyloric tumour was found at operation and the standard Fredet–Rammstedt pyloromyotomy was carried out. Pre- and post-operative routines corresponded with the generally accepted techniques, and need no further consideration here.

Clinical Aspects.—A study of the case reports in Tables I and II shows that, with the exception of a rather late onset of vomiting in some cases, congenital pyloric stenosis, as so far reported in African infants, does not differ in its clinical aspects from the condition as it occurs in other races. The point is worth making, as cosmopolitan diseases do not always manifest themselves identically in different peoples. Two instances of

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this are peptic ulcer and intussusception, which in Southern Nigeria differ greatly in their natural histories from the same diseases as they occur in Europe and America.

Incidence in Africa

The question arises whether congenital pyloric stenosis is a rare disease in the African infant or whether it only seems to be so. In West Africa, and no doubt in many parts of Africa, it is almost impossible to assess the incidence of various diseases. A definite but unknown proportion of the population do not accept orthodox medical practice, and in the more remote areas a further unknown proportion are out of reach of such attention. Because of the widespread shortage of doctors, many hospital out-patient departments are grossly overcrowded, and the time the doctor can give to the individual out-patient is very limited.

The clinical picture of congenital pyloric stenosis is characteristic, and the diagnosis is based on the triad of signs and symptoms: projectile vomiting, visible gastric peristalsis, and a palpable pyloric tumour, occurring in the early weeks of life. But much time and patience are often required to palpate the elusive tumour, without which a certain diagnosis cannot be made, while visible gastric peristalsis is often periodic in its appearance. It is all too easy to treat symptomatically the vomiting with which the infant presents, and to overlook the other signs, which, in any case, are not present in the early stages. Under the conditions prevailing in many African out-patient clinics, and bearing in mind that vomiting due to various causes is the presenting symptom in a large proportion of the infants attending them, the diagnosis of congenital pyloric stenosis is apt to be missed, and it may be assumed that many more cases occur than the literature would suggest.

With the expansion of medical services now taking place in most parts of Africa, and with greater awareness that the condition does occur in the African infant, there will certainly be an increase in the number of cases diagnosed and reported. On the other hand, the scarcity of reported cases to date is remarkable, and most of the authors quoted in Table I stated that the

TABLE I.—*Previously Recorded Cases of Congenital Pyloric Stenosis in African Infants*

Case	Author	Territory	Tribe	Sex	Birth Order	Age at Onset of Vomiting	Projectile Vomiting	Constipation	Dehydration	Malnutrition	Visible Gastric Peristalsis	Palpable Pyloric Tumour	Treatment	Result
1	Petcher (1953)	N. Nigeria	Laka	—	—	3 weeks	+	+	+++	+++	+	+	Pyloromyotomy	Cured
2	Petcher (1953)	,,	Kilba	—	—	3 ,,	+	+	+++	+++	+	+	Operation refused	Died
3	Shepherd-Wilson and Gelfand (1955)	S. Rhodesia	—	M	2nd born	4 ,,	+	+	+++	+++	+	+	Pyloromyotomy	Cured
4	Luder (1956)	E. Africa	Ganda	M	3rd ,,	2 ,,	0	+	0	0	+	+	,,	,,
5	Griffiths (1956)	S. Africa	Bantu	M	—	3 ,,	—	—	—	—	—	—	,,	—
6	Hamilton (1957)	Uganda	Dama	M	—	2 ,,	+	+	+	−	+	+	,,	Cured
7	Menezes and Thethravusamy (1957)	Zanzibar	Nyagatwa	F	3rd born	3 ,,	+	+	++++	+++	+	+	Medical	,,
8	Scragg (1958)	S. Africa	Bantu	M	1st ,,	Unknown	+	+	+	++	+	+	Pyloromyotomy	Died from post-operative pneumonia
9	,,	,,	,,	M	1st ,,	5 days	+	+	+	++	+	+	,,	Cured
10	,,	,,	,,	M	1st ,,	5 ,,	+	+	+	++	+	+	,,	,,
11	Boroda (1960)	E. Africa	Mudande	M	2nd ,,	3 weeks	0	++	0	0	+	0	,,	,,

+ = Positive finding. 0 = Negative finding. — = Finding not recorded. (Where more than one value is reported, the values given represent the extremes.)

TABLE II.—*Newly Reported Cases of Congenital Pyloric Stenosis in Nigerian Infants*

Case	Hospital and Date	Tribe	Sex	Birth Order	Age at Onset of Vomiting	Projectile Vomiting	Constipation	Dehydration	Malnutrition	Visible Gastric Peristalsis	Palpable Pyloric Tumour	Treatment	Result
1	Adeoyo Hospital, Ibadan. April, 1957	Bini	M	1st born	3 weeks	+	++	+	+	+	+	Pyloromyotomy	Cured
2	University College Hospital, Ibadan. April, 1958	Yoruba	M	1st ,,	7 ,,	0	++	+++	+++	+	+	,,	Collapsed and died 24 hours after operation. P.M. did not reveal cause of death
3	University College Hospital, Ibadan. Aug., 1959	Ibo	M	5th ,,	8 days	0	+	+	0	0	+	,,	Cured
4	University College Hospital, Ibadan. Feb., 1960	Yoruba	M	1st ,,	6 weeks	+	+	++	++	+	+	,,	,,
5	University College Hospital, Ibadan. April, 1960	,,	M	1st ,,	2 ,,	+	+	0	0	+	+	,,	,,
6	University College Hospital, Ibadan. June, 1960	Urhobo	M	3rd ,,	4 ,,	+	+	0	0	+	+	,,	,,
7	General Hospital, Lagos. Nov., 1958	Yoruba	M	4th ,,	5 ,,	+	++	+++	+++	+	0	,,	,,
8	General Hospital, Lagos. Nov., 1959	,,	M	—	1 week	0	+	+	0	+	+	,,	,,
9	General Hospital, Enugu. Jan., 1959	Ibo	M	—	10 weeks	—	—	—	—	—	—	,,	,,
10	General Hospital, Enugu. Sept., 1959	,,	M	—	—	—	—	—	—	—	—	,,	,,

+ = Positive finding. 0 = Negative finding. — = Finding not recorded. (Where more than one value is reported, the values given represent the extremes.)

cases they recorded were unique in their experience. Bowesman (1960), in his book on surgery in the tropics, remarks that in twenty years of surgical practice in Africa he has operated on only six African babies for congenital pyloric stenosis. The town of Ibadan in Western Nigeria, with a population of over 750,000, is served by two large public general hospitals—University College Hospital and Adeoyo Hospital. The former has a large specialist paediatric unit, and in the latter separate children's out-patient clinics are held. If the incidence of congenital pyloric stenosis in Ibadan approached the European level of three or four cases per thousand births, it seems likely that many more than six cases would have been diagnosed between the two hospitals during the past three years. While the evidence is inconclusive, it suggests that the condition is relatively uncommon in the African infant.

Incidence in American Negroes

A consideration of the incidence of the disease in American negro infants is of obvious interest. The American literature does not appear to contain any study devoted to the subject, though various authors refer to it. Ward (1927) found no cases reported in American negro infants before 1927. Gleich and Goodman (1930) reported two cases in negro infants, and Donovan (1932) found two such infants in a series of 119 cases. Of 76 cases of congenital pyloric stenosis treated at the Charity Hospital, New Orleans, between 1916 and 1936 Romano and McFettridge (1938) found 30% to be negro infants. Ladd, Ware, and Pickett (1946), reporting on a series of 380 cases of the condition operated on between 1939 and 1945 at Harvard Medical School and the Children's Hospital, Boston, noted no racial disposition in their series. They ascribed the fact that they had never seen a case in a negro infant to pure chance. Mitchell-Nelson (1946) stated that the condition was apparently rare in negro infants. Gross (1953), in a presentation of the subject of congenital pyloric stenosis based on experience gained from the operative treatment of 1,787 cases up to December, 1952, stated that there was no racial predisposition to the condition, but did not state what proportion, if any, of his cases occurred in negroes. English *et al.* (1954) found 7 negro infants in a series of 41 cases operated on at the Boston City Hospital between 1949 and 1952. Benson and Warden (1957) reported from Michigan that, of their consecutive series of 707 cases operated on between 1940 and 1955, 63 were coloured infants, and that in their hospital admissions the ratio of coloured to white patients was roughly one to two.

These are all the references to the subject that a search of the available American literature reveals, and it is difficult to draw firm conclusions from them. They show that an increasing number of cases of congenital pyloric stenosis occurring in American negro infants have been reported over the past three decades, but no figures are given to show what relation the incidence of the condition bears to total births in this racial group. There are therefore no grounds for supposing that there has been an actual increase in incidence, and it seems likely that the increase in the number of cases reported is related directly to the expansion of medical services in America during the period concerned. In fact, the number of cases reported seems very small in relation to the large negro population in America.

In conclusion, it is suggested that congenital pyloric stenosis is a relatively rare condition both in the African and in the American negro infant, and that this may be due to a common genetic factor.

Summary

A total of 11 cases of congenital pyloric stenosis occurring in African infants have previously been described. A further 10 cases diagnosed in Nigerian infants over the past three years are reported.

The literature dealing with the occurrence of the condition in African infants and in American negro infants is reviewed.

The condition, as so far reported in African infants, does not appear to differ in its clinical aspects from the disease as it occurs in other races.

Congenital pyloric stenosis appears to be relatively rare both in the African and in the American negro infant, and this may be due to a common genetic factor.

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The proposed hospital at Lusaka, which is to be built at a cost of around £190,000, will provide accommodation for mentally defective Africans for whom there are no specialist hospital facilities at present in Northern Rhodesia. There will be three quadrangular blocks, housing altogether 316 patients, in the form of dormitories accommodating up to 25 patients. Each block has its own treatment, recovery, and occupational therapy departments. A central boiler-house supplies steam to each block to give hot water by means of calorifiers. There is a central kitchen with subsidiary kitchens in each block. The separate administrative block contains the pharmacy and a laboratory, as well as the various offices. Other buildings are a central laundry, stores, and mortuary. The hospital will be staffed by members of religious orders, and the male and female quarters have been designed accordingly. Separate housing is being provided for the medical superintendent and the hospital secretary. A hostel for female African staff and 26 houses for the male African staff are also being provided.

CONGENITAL AGAMMAGLOBULINAEMIA

REPORT OF TWO FURTHER CASES

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Agammaglobulinaemia was first recognized in 1952 by Bruton as a distinct syndrome manifested by severe recurrent bacterial infections associated with an absence or severe deficiency of circulating gamma-globulin but a normal total serum protein. Since then several further cases have been reported in the world literature, and in 1955 the Medical Research Council set up a working party to collate the findings and advise on the problems arising in cases diagnosed in Great Britain. Nevertheless, there is still a lack of agreement on many points, and we therefore feel justified in reporting two further cases.

We agree with Firkin and Blackburn (1958) in defining agammaglobulinaemia as that condition in which circulating gamma-globulin is not demonstrable by the technique of electrophoresis, while recognizing that in many such cases very small amounts of gamma-globulin may be shown to be present by the more sensitive immunological method. The definition will usually exclude the physiological state, which occurs in the first few months of life, when the gamma-globulin commonly falls to between 300 and 600 mg./100 ml., although two cases have been reported in which it fell as low as 75 and 150 mg./100 ml., before beginning the climb towards the normal levels of 700 to 1,500 mg./100 ml., usually but not always reached by the age of 12 months. Also excluded by definition is the hypogammaglobulinaemia associated with hypoproteinaemia, such as occurs in nephrosis, where it has been suggested that the low gamma-globulin is at least partly responsible for the tendency to recurrent infection in that condition.

Recent evidence strongly suggests that the agammaglobulinaemia is itself a secondary effect of a more primitive, probably enzymatic, inborn error, as certain of the clinical features, notably the ability to accept homografts, do not seem to be dependent upon the lack of gamma-globulin (Medawar, 1955). Furthermore, it appears that some beta-globulins at least are also deficient. It is probably better to await further information on the nature of the primary defect, which may reside in the primitive reticulum cell, before embarking on a new terminology, among which immuno-globulinaemia and immune paralysis have been suggested.

Case 1

The patient was seen at the Walsall Manor Hospital on June 18, 1958, at the age of 11 months. In February he had developed an illness diagnosed as whooping-cough by the family doctor. Since then he had had a constant dry cough and his weight had fallen from 18¼ to 16½ lb. (8.3 to 7.5 kg.). In March, and again in May, he had had two distinct febrile illnesses diagnosed as tonsillitis. For four days he had been vomiting and for two days had been passing watery stools, though this was tending to improve.

On examination he was pale and fretful. There were scattered rales in his lungs. His haemoglobin was 9.6 g./100 ml. Chest *x*-ray examination showed only a hilar adenitis and his tuberculin test was subsequently found to be negative. A rectal swab grew no pathogens. A simple sedative mixture was prescribed, and it was felt that he might indeed have had whooping-cough and two intercurrent illnesses before he had completely recovered from the original attack of pertussis.

On July 3 he was admitted as an emergency case. His cough was much more severe, the diarrhoea had returned, and for two days he had been running a high fever, which had not responded to antibiotics. He had lost a further 1¼ lb. (567 g.) in weight, was toxic and dehydrated with a temperature of 105° F. (40.6° C.), and had a respiratory rate of 50. Again, only scattered rales were heard, but bronchopneumonia was diagnosed and penicillin and streptomycin were given intramuscularly. By next morning he was gravely ill. It was then found that his urine was loaded with sugar and his blood sugar was 250 mg./100 ml. He was given crystalline insulin 10 units at once and 5 units hourly until the urine became sugar-free 12 hours later and, by intravenous drip, a pint (570 ml.) of glucose-saline followed by half a pint (284 ml.) of half-strength plasma. At this stage we learnt that his total white blood cells were 850/c.mm., of which only 80 were granulocytes. In view of this, after further glucose-saline, half a pint (284 ml.) of blood was transfused.

He slowly improved, his temperature falling to between 99 and 100° F. (37.2 and 37.8° C.), but his distressing cough persisted and he was restless and miserable. Chemotherapy was discontinued on July 10. On July 16 his diarrhoea recurred, but it responded to neomycin. On July 20 he had a relapse of the bronchopneumonia, and on this occasion haemolytic streptococci were found in his cough swab. Meanwhile fibrocystic disease of the pancreas had been excluded and agammaglobulinaemia was considered. His blood group was A, and no iso-agglutinins could be detected in the serum. An electrophoretic strip showed the apparent absence of gamma-globulin, though Dr. Soothill, of the department of experimental pathology, University of Birmingham, was subsequently able to demonstrate a level of 80 mg./100 ml. Plasma cells being characteristically reduced or absent in agammaglobulinaemia, bone-marrow from a sternal puncture was carefully searched. No plasma cells could be found.

On July 26, the case having been accepted into their series by the Medical Research Council, intramuscular injections of gamma-globulin were started in alternate 17-week courses of 0.025 and 0.5 g./kg. of body weight. At the beginning of this treatment he weighed only 14 lb. (6.4 kg.) and, although there was no definite illness, he was not well. His subsequent general improvement was rapid and he put on weight. He has remained well, except for frequent episodes of upper respiratory catarrh and a short bout of diarrhoea in December, 1958, which responded readily to treatment. His circulating gamma-globulin is usually between 80 and 160 mg./100 ml.

Case 2

The patient was admitted to the George Eliot Hospital, Nuneaton, on January 23, 1958, at the age of 6 months. For two weeks he had been unwell with listlessness, cough, and pyrexia. On admission he was acutely ill; temperature 105° F. (40.6° C.), pulse 140, and respirations 48. He had respiratory distress and signs of a bilateral bronchopneumonia, which were more marked on the right. An *x*-ray film of his chest was reported as showing massive consolidation in the right lower zone. His distress was somewhat relieved by oxygen. Penicillin 250,000 units six-hourly and streptomycin 250 mg. 12-hourly, both given intramuscularly, were started.

His condition improved slowly, and when on January 27 his Mantoux was found to be positive isoniazid 15 mg. was given six-hourly by mouth in addition. On February 2 the

penicillin was discontinued, the other therapy being maintained until June 19. By February 19 he was very much improved and his chest *x*-ray picture was reported as showing advanced resolution of the pneumonic consolidation. His progress thereafter was punctuated by recurrent, acute though not severe, respiratory infections, shown clinically by a rise of temperature to the region of 103° F. (39.4° C.), signs of a bronchitis, and radiologically by basal pneumonic shadowing. His weight, which on admission was 13¾ lb. (6.2 kg.), increased slowly, so that at the age of 12 months he weighed 18¾ lb. (8.5 kg.).

By this time investigation of his contacts had shown his father to have open tuberculosis. His three siblings were found to have positive Mantoux reactions but radiologically no evidence of tuberculosis. Among other investigations of the patient, tubercle bacilli were not recovered in three pharyngeal swabs, and serial E.S.R.s (Westergren) gave the following results: January 29, 5 mm. in one hour; February 5, 2 mm., and February 8, 2 mm.

On July 17 electrophoresis of his serum had shown a complete absence of gamma-globulin, and a separate determination by Dr. Soothill gave a level of 3 mg./100 ml. On September 12, weekly injections of gamma-globulin were started under the same M.R.C. regime as in Case 1. Since then he has had coryza only occasionally, and one attack of diarrhoea during which no pathogenic bacteria or viruses were isolated from the stools. Levels of gamma-globulin have varied from 100 to 160 mg./100 ml.

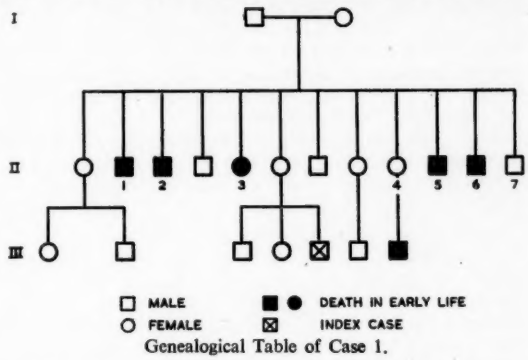
In retrospect we feel that the tuberculous element in his illness was probably slight because of the rapidity of response, both clinical and radiological, to therapy and also because of the failure to recover tubercle bacilli.

Family History

It is generally stated that this condition depends upon the presence of a sex-linked recessive factor, which is transmitted by females and manifested in males, though this view is not universally accepted. The siblings of both these children have normal levels of gamma-globulin. Case 2 comes from a widespread Irish family, and unfortunately it has not been possible to determine this child's family history in detail. His father had seven siblings and one half-brother, and, so far as is known, all are alive and well. His mother had 10 siblings. One had died aged 7 years from pneumonia after an illness lasting two weeks and another at an unknown age, of "purple measles." Both were boys.

In the family of Case 1 there is nothing relevant on the paternal side. His mother comes from a large family, and it was possible to obtain the maternal pedigree in detail. His grandparents were only-children and unrelated. Of their 12 children, four boys and one girl died in early life. As the most recent death was in 1938, agammaglobulinaemia could not then have been considered, and the stated causes and ages at death were as follows: (1) epidemic enteritis—1 month; (2) prematurity—a few hours; (3) acute enteritis—10 months; (5) bronchopneumonia—12 months; (6) bronchopneumonia with measles — 21 months. Agammaglobulinaemia could not have been a significant factor in II 2, as he lived only a few hours and II 3 was a female. II 7 has had a lobectomy for bronchiectasis, but his electrophoretic strip is normal.

In the third generation there has been one death, the son of II 4. This boy came under the care of one of us (J. M. G.) when he was admitted with bronchopneumonia to the Manor Hospital, Walsall, in December, 1957, at the age of 4 months. He was extremely ill on admission, initially requiring continuous oxygen. *Staphylococcus pyogenes* was isolated from a cough swab. It was resistant to all the common antibiotics with the exception of erythromycin, to treatment with which he responded. He also had a systolic murmur consistent with a congenital lesion of the heart, to which the unusual severity of his illness was partly attributed. After his discharge from hospital contact with him was lost. He was admitted to another hospital



Genealogical Table of Case 1.

at the age of 11 months and died within an hour. The stated cause of death was bronchopneumonia, but unfortunately a post-mortem examination was not carried out.

This pedigree is not inconsistent with a sex-linked recessive mode of inheritance.

Discussion

The infections to which these children are peculiarly susceptible are those associated with the common pyogenic organisms, staphylococcus, meningococcus, pneumococcus, haemolytic streptococcus, and also haemophilus. In general, infections by Gram-negative organisms are withstood better than those by Gram-positive organisms. The occurrence of diarrhoea has been emphasized by Firkin and Blackburn (1958) and mentioned also by McKay and Richardson (1959). Case 1 had at least two such attacks and Case 2 had one. The response to tuberculous infections presents a striking contrast in that the acquired immune reaction to the tubercle bacillus seems to function normally, suggesting that tuberculosis differs immunologically from other bacterial infections. The case described by Elphinstone *et al.* (1956) had a positive Mantoux reaction, as also had Case 2.

On the whole these children withstand virus infections normally. Cases have been reported in which intercurrent attacks of rubella, rubeola, mumps, chicken-pox, infective hepatitis, and poliomyelitis have followed the usual course. Moreover, the acquired specific immunity after attacks of measles and chicken-pox has been shown, since further intimate contact with the same virus has failed to cause second attacks, in spite of the fact that specific antibodies have not been detected in the serum. Both of our cases failed to show a significant increase in antibody titre after an "immunizing" course of poliomyelitis vaccine.

In contrast to the normal clinical response to infections with these viruses, there have been reports of death from generalized vaccinia. Such reports include the case described by Keidan *et al.* (1953), which does not, however, appear to have been a typical case of congenital agammaglobulinaemia; and that described by Kozinn *et al.* (1955) is difficult to evaluate as the haemagglutination

inhibiting test was positive. There remain, however, the single cases described by Somers (1957), by Sédallian *et al.* (1957), and by Galloway and MacBean (1958). However, other authors—for example, Apt (1953–4)—report patients vaccinated without complications. One wonders whether secondary infection could have been a factor in the fatal cases. One is also surprised that Galloway and MacBean state that the overall mortality rate in generalized vaccinia is 90%, which does not agree with our small experience. Nevertheless, in our present uncertain state of knowledge we do not feel that vaccination is a justifiable procedure in the presence of agammaglobulinaemia.

It may be that agammaglobulinaemia is not such an uncommon condition as it seems. Good and Varco (1955) were able to collect six cases in 10 months, and three were seen at the Mayo Clinic in seven months (Hayles *et al.*, 1954). We have on many occasions before and since looked for it in children, who have had several attacks of pneumonia before their first birthday or in whom there is an appropriate family history, without finding a further example. The case of the son of II 4 (see above) suggests that they may go unrecognized at times when bronchopneumonia is epidemic. Obviously the more cases that are investigated the more examples will be found, but there seems nothing in the examination of the child with this condition particularly to draw one's attention to the correct diagnosis.

Margulis *et al.* (1957) have suggested that the chest radiograph may be of potential diagnostic importance when with extensive parenchymal involvement there is a paradoxical absence of hilar lymph-node enlargement. That these features, which are shown by the serial radiographs in Case 2, are not invariable was demonstrated in Case 1. As mentioned previously, his chest radiograph in June had shown a right hilar adenitis, which by the following month was so marked that the radiologist suggested that tuberculosis should be considered. The case described by Elphinstone *et al.* (1956) showed on one occasion "a little enlargement of the right hilar shadow only." His sibling, who also had agammaglobulinaemia, developed enlargement of the regional lymph nodes in response to B.C.G. vaccination.

The normal sedimentation rate of Case 2 at a time when one would have expected it to be markedly raised might in retrospect have been of some diagnostic significance. This was also found by Elphinstone *et al.* and has been commented upon by several other authors. Citron (1957), however, in describing a case of acquired agammaglobulinaemia in a girl of 12, where no gammaglobulin was detectable by paper electrophoresis, states that the sedimentation rate "was moderately raised during infection except in the last few weeks before death, when in spite of much pulmonary infection the E.S.R. was 3 mm. per hour or less." It is, however, not clear from his paper what the time relationship was between the raised E.S.R. and the discovery of the absence of gamma-globulin. It would perhaps be unwise at present to regard the low E.S.R. found in these cases as being due solely to low gamma-globulin, since the rate of sedimentation is known to be influenced also by the alpha-globulin and fibrinogen levels in the plasma.

Summary

Two cases of agammaglobulinaemia are described. Their family history is consistent with a sex-linked recessive mode of inheritance. The problems of diagnosis and the response of these cases to different types of infection are discussed.

Among others, we wish to thank Dr. F. O. MacCallum, of the Virus Reference Laboratory, Dr. P. O. Williams, of of the Medical Research Council, and several of our colleagues for their help in the diagnosis and treatment of these cases. We are particularly indebted to Professor J. R. Squire and the senior staff of the department of experimental pathology, University of Birmingham, for their continual assistance and encouragement.

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TOXIC EPIDERMAL NECROLYSIS

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The paper by Catto (1959) reporting a case of toxic epidermal necrolysis in a boy aged 3, has directed attention to the syndrome described by Lyell (1956) and by Lang and Walker (1956, 1957), and has again raised the question of aetiology. The available evidence indicates that the characteristic clinical picture is a response to a variety of circulating toxins or allergens, derived from drugs or possibly from foods—for example, snoek liver—but the causative role of the suspected agents has not hitherto been definitely established.

In the cases reported below, known drugs are believed to have precipitated the typical syndrome on more than one occasion in persons who were already sensitive to them : these drugs were phenolphthalein and dapsone.

Case 1

In December, 1959, a deeply pigmented Nigerian woman, aged about 55, was admitted to the Uzuakoli Research Unit Clinic suffering from a widespread papular eruption of four days' duration. The illness had been ushered in by headache, nausea, and general malaise. The temperature and pulse were only slightly raised, and the patient's general condition was good. The skin presented the following picture: a purplish-black discoloration of the whole face, including the lips, but sparing the nose and the periphery ; large macular hyperpigmented areas on the trunk roughly symmetrical in distribution ; a diffuse slate-grey dyschromia of the skin of the limbs. The buccal, nasal, and meatal mucosae and the conjunctivae were unaffected. This hypermelanosis had appeared some months previously ; during the present illness the areas involved had become acutely tender to the touch.

Sedatives and calming applications were prescribed, and prednisolone ("deltacortril" tablets) was given. The subjective improvement was satisfactory, the pruritus and malaise diminishing.

On the fourth day after admission, however, the patient became restless, and the temperature rose rapidly to 104° F. (40° C.). Large areas of skin on all four limbs became detached as if scalded; they could be slid over the subjacent tissue, just as a rubber glove, put on wet, can be slid on the fingers. Nikolsky's sign was positive over adjacent areas of skin not visibly separated. Its elicitation resulted in painful and persistent formication. The temperature remained raised for three days before beginning to return to normal; during this time the patient felt and looked ill. Then, from deltoid to finger-tips and from trochanters to toes, the whole skin peeled off in large sheets, revealing a surface slightly moist and dull pink in colour. The skin of the palms, soles, and pre-tibial regions was the last to separate, but it, too, was shed eventually.

While the skin was peeling, the patient's general condition was very good: the temperature was normal, and she preferred to be ambulant. The underlying skin was soft and supple like that of a newborn coloured baby, but of a more dusky hue than normal. The whole denuded surface repigmented rapidly and uniformly; there was no perifollicular or marginal repigmentation. After three weeks the skin of the limbs had assumed its pre-existing slate-grey colour. Meanwhile the skin overlying the hypermelanotic macules on the face and trunk had desquamated in small flakes, the underlying macules becoming blacker.

Previous History.—Careful interrogation of the patient and her relatives disclosed that two precisely similar episodes had occurred—in 1955 and in June, 1959. The chain of events had been identical: a "fever" for which she had been self-treated on both occasions with aspirin, mepacrine, and proguanil. Shortly afterwards she experienced a generalized irritation, and then the superficial epidermis became detached from all four limbs. The dark areas on the face and trunk appeared; they had faded slightly before becoming darker during the second attack. In the absence of clinical notes, the observations of a son-in-law (a medical auxiliary) have been most valuable, but the "fever" from which she originally suffered cannot be accurately diagnosed in retrospect. The "fever" she remembers most vividly is that associated with the epidermolysis.

Prolonged inquiry failed to incriminate any article of diet, or garment, or skin infection, or contact with plants that might have precipitated the syndrome in all three apparently identical episodes; no hormonal change (puberty, pregnancy, menopause) was operative; the only common factor appeared to be the drugs that she and her relatives admitted she had taken.

Subsequent History

In May, 1960, in an attempt to identify the drug responsible—if such were indeed the case—patch tests were performed in turn with all the drugs she had taken before the occurrence of the epidermolysis. When these tests had proved negative, a small dose of each drug was given by mouth, with negative results. It then transpired that some tablets of sulphathiazole had also been administered by a son as a "tonic"; tests with this product, however, also proved negative.

Some days later, while still under observation, the patient took a proprietary laxative tablet containing 5 gr. (320 mg.) of phenolphthalein. Within 30 minutes she complained of generalized pruritus, and one hour later small papules appeared over the entire skin, closest-set on the limbs. The irritation became more intense, especially in the hypermelanotic areas. The patient affirmed that she felt exactly as she had done on each of the three previous occasions.

That evening the temperature rose to 102.2° F. (39° C.) and the pulse to 88. The urine was normal chemically and microscopically. The total white count was 5,500/c.mm. (22% neutrophils, 54% lymphocytes, 24% eosinophils). The stools were normal, apart from the presence of hookworm eggs. Prednisolone was administered and calamine lotion was applied to the skin. Within 72 hours the temperature and pulse had returned to normal and the irritation had diminished considerably. The prednisolone was gradually reduced.

Seven days after the aperient tablet had been taken, however, the patient complained of all the symptoms of relapse. The temperature rose to 103.2° F. (39.6° C.) that evening, and a degree higher the following evening. The skin of the limbs was tender on palpation, and the superficial layers were beginning to loosen. The temperature and pulse again returned to normal within four days, and the skin irritation and tenderness ceased. The integument became detached in the same situations as before, and in the same sequence. The underlying surface was dull pink in colour and quite dry when the epithelium had become completely separated. The hairs remained intact in their follicles. At no time was there any pus formation or ulceration. No antibiotics or sulphonamides were given. There was no scabbing or scarring.

On subsequent interrogation the son admitted that before each of the three episodes he had given his mother different proprietary laxative preparations each containing phenolphthalein as the active ingredient. When first questioned he had not mentioned this fact, because he did not think that such products were "drugs" or "medicines."

After the patient's recovery, further patch-tests were performed. The site of a hypermelanotic macule showed slight delayed (48 hours) sensitivity to 1% alcoholic phenolphthalein; controls in normal skin, and in the skin of the forearms, showed no reaction.

Comment

In the general population of Eastern Nigeria phenolphthalein in proprietary laxatives is the commonest cause of a fixed drug eruption characterized by hypermelanotic macules, but the incidence of sensitivity to the product is unknown: it is probably very low. In the past 10 months, however, one of us (S. G. B.) has been consulted by 10 persons complaining of a fixed drug eruption that proved on investigation to be due to phenolphthalein, and one of these (Case 1) has developed epidermal necrolysis.

Case 2

A well-built Nigerian woman of about 37 years, and weighing 128 lb. (58 kg.), had been receiving standard treatment with dapsone for tuberculoid leprosy since March, 1956, having first noticed the leprosy lesions about a year previously. She attended, somewhat irregularly, the Kakwagom Leprosy Treatment Centre twice weekly as an out-patient, receiving 400 mg. of dapsone orally at each visit. This maximum dose had been reached in accordance with the dosage schema commonly followed: the initial dose of 100 mg. twice weekly for four weeks was followed by 200 mg. twice weekly for four weeks, then by 300 mg. twice weekly for four weeks, and 400 mg. twice weekly thereafter.

At the end of February, 1960, the patient complained of malaise, "fever," and a generalized papular eruption. Large flaccid blisters made their appearance on the face, trunk, and limbs. She had taken no drug but dapsone.

She was seen by one of us (E. R.) on March 1, and was admitted to Ogoja Leprosy Settlement Hospital. By this time the superficial epithelium in the affected sites had ruptured, releasing a little yellowish fluid. The denuded surfaces were covered by an intact layer of moist epithelium, slightly red in places from punctate capillary exudation, and distinctly blacker than the normal dark-brown skin. The superficial layers of the skin of the arms below the insertion of the deltoid, and of the legs, were almost completely separated from the deeper layers, and could be slid over them. Where no cleavage was apparent to the eye, Nikolsky's sign was present. The pretibial skin was still intact, and Nikolsky's sign could not be elicited here.

Apart from the skin, the patient's general condition was very good. Nothing abnormal was found on routine clinical examination; in particular, the liver was not palpable, and there was no jaundice. The urine contained a trace of albumin.

Dapsone was stopped at once, and antihistamines were given. Calamine lotion was freely applied to the blisters and to the limbs. To anticipate the supposed risk of infection, penicillin was given intramuscularly. The severe degree of anaemia present (haemoglobin, 50%; R.B.C., 2,370,000/c.mm.) was treated with iron. The white blood count showed no abnormal features, apart from an eosinophilia of 10%.

When the patient was examined by both of us on March 10 the only remaining evidence of the flaccid superficial blisters was the presence of hypermelanotic macules on the face and trunk. Except on palms and soles and pretibial region, the skin of the limbs was detached in large continuous sheets, revealing a diffusely hyperpigmented underlying surface.

Prednisolone was given from March 10 onwards for 14 days, decreasing latterly. Apart from the residual hypermelanosis—macular and discrete on face and trunk, and diffuse on the limbs—the patient had completely recovered within four weeks of the onset of the incident. There had been no ulceration, and there was no scarring.

Treatment with dapsone was resumed, with the same cautious build-up as when treatment was begun four years previously. There was no recurrence of pruritus, no papular rash, and no excerbation of the hypermelanosis.

Three months later the patient was again examined at the Leprosy Treatment Centre. She had been taking full doses of dapsone (400 mg. twice weekly) without any untoward symptoms. The hypermelanosis was unchanged, both in extent and in degree.

Previous History.—Interrogation of the patient disclosed the fact that she had previously experienced two similar episodes since she began taking dapsone—the first after about a year's treatment, and the second after two years. On each occasion she had absented herself from attendance at the Leprosy Clinic. She had recovered completely from both attacks, and stayed in her isolated village, 30 miles from the nearest doctor. After the first episode she noticed the black patches on her face and trunk and the general darkening of the skin of the limbs.

It would seem that during the second and third attacks the loss of the superficial epithelium occurred in precisely the same situations—namely, at the sites of the discrete hypermelanotic macules, and, more extensively and superficially, from all four limbs.

Comment

The history of one or more attacks of generalized papular dermatitis, followed by the appearance of the hypermelanotic macules of a fixed drug eruption, is a not uncommon manifestation of sensitivity to dapsone. Sometimes the macules appear *de novo*, with no ascertainable preceding pruritus or exanthem, or suggestion of local inflammation. In some individuals a single tablet of dapsone (100 mg.) has precipitated the condition; whereas in others a period of cumulation seems to be necessary before some threshold is passed and sensitization develops.

The subsequent course of events varies also. Sometimes the hypermelanotic macules behave as a fixed drug eruption, with local symptoms (pain, tenderness, erythema, infiltration, bullae formation, exacerbation of the hypermelanosis) with each subsequent administration of the drug. More often, however, once the initial acute stage is over the patient may continue to take the drug without ill effects. In such a disease as leprosy, in which treatment is imperative, perseverance with therapy without incommoding the patient unduly has revealed different types of reaction that would remain unknown if an optional treatment (like, for example, phenolphthalein given as an aperient) had been abandoned after signs of hypersensitivity had become manifest.

When symptoms persist, or recur with further antileprosy treatment, slow desensitization with aqueous solapsone is often successful.

The fatal dermatitis observed in the early high-dosage dapsone treatment for leprosy seems usually to have been an exfoliative dermatitis (Barnes, 1960, personal communication) or, rarely, an erythema multiforme of the Stevens–Johnson type, associated with jaundice and albuminuria. No cases similar to the present are recorded.

In a total population of 45,035 persons in the Belgian Congo, 160 cases of hypermelanosis were observed in 5,349 patients undergoing treatment for leprosy with dapsone or solapsone by mouth or by intramuscular injection (Browne, 1959). In Nigeria, 19 examples have been encountered in approximately 550 cases of leprosy (Browne, 1960).

Case 2 is the only one in which the intra-epidermal cleavage characteristic of toxic epidermal necrolysis has occurred.

Discussion

The symptomatology and clinical course of the disease in the two patients resemble so closely the findings in published cases of toxic epidermal necrolysis in most respects that detailed comment on this score is unnecessary. In particular, the appearance of the denuded surface, the minimal exudation in the extensive flaccid blisters, and the subsequent absence of pus formation, all indicate the superficial level of the cleavage. The clinical gravity of reported cases appears to vary: three out of 10 cases were fatal; five had recurrent attacks of a similar type.

Several points of interest and importance, however, call for some notice. Firstly, the characteristic syndrome was precipitated by known chemical compounds in subjects whose skin already gave evidence, by the presence of hypermelanotic macules of a fixed drug eruption, of sensitivity to these compounds. It is noteworthy that a similar manifestation of sensitivity in the two patients should be followed by the same syndrome of epidermolysis involving the same areas of skin. A similar hypermelanotic fixed eruption has been observed in Nigeria in connexion with mepacrine, "acetylarsan," thiacetazone, diphenylthiourea, and dithio-*iso*-phthalate; and similar cutaneous lesions have been observed after a contact dermatitis associated with photosensitivity and caused by unidentified purgatives of vegetable origin. No case of toxic epidermal necrolysis has been observed in these patients.

Secondly, the epidermolysis in these two cases appears as a superimposed manifestation of sensitivity to such drugs. In the case of both phenolphthalein and dapsone, cutaneous reactions may show wide variations: erythrodermia, papulo-erythematous eruptions, erythema bullosa, and the Stevens–Johnson syndrome. The commonest eruption is a localized erythema, followed by a discrete or diffuse hypermelanosis; more rarely, there is a severe generalized exfoliative dermatitis which may prove fatal (Lowe, 1950; Allday and Barnes, 1951; Barnes and Barnes,

1951). Cases have been seen by both of us in phenolphthalein-induced and dapsone-induced fixed eruptions showing small bullae; when the epithelium has been removed by scratching, a sky-blue macule remains, which later becomes slate-grey when the pigmented basal layer is reconstituted (Browne, 1959). In such cases the bullae are set deep in the dermis and are tense with fluid.

Thirdly, in both cases reported above, administration of the drugs resulted in an exacerbation of the pre-existing hypermelanosis caused by the same drug, and this exacerbation was accompanied not only by a recurrence of the generalized papular eruption but also by the characteristic intra-epidermal cleavage in the areas of predilection. In the first case each known administration of the drug was followed by the syndrome, whereas in the second case irregular twice-weekly ingestion of dapsone resulted in three distinct but similar episodes. The diffuse slate-grey pigmentation of the limbs indicates a widespread deposit of melanin, mainly in the papillary layer of the dermis—a post-inflammatory phenomenon.

Fourthly, these cases seem to furnish a clinical link between the epidermolysis occurring in apparently healthy persons and the varieties of toxic erythemata. The actual cutaneous manifestations in a given individual depend on the precise level of skin predominantly affected: at one time the cutaneous target is superficial, leading to cleavage in an intra-epidermal plane; at other times the target is deeper, becoming apparent clinically as a hypermelanosis or as a bullous eruption. The present cases conform to the published descriptions in that there was superficial denudation of very extensive areas of integument, in contrast with the commoner type of recurrent fixed drug eruption in which discrete deep-seated bullae occur in an erythematous skin. Why the target for the toxic onslaught in any one patient should be the superficial layers of the epidermis at one moment and the deeper layers at another, or both simultaneously (as in the first case report), is a matter for speculation.

The virtual absence of constitutional symptoms (after the initial pyrexia and generalized malaise) in both patients while they were undergoing the loss of extensive areas of skin is in striking contrast with the shocked condition of cases of scalding in which comparable areas are involved, or of cases of Stevens–Johnson syndrome in which severe toxic absorption from involved mucosae and infected denuded skin occurs. The fatal published cases of the syndrome appear to have been complicated by this type of infection.

Fifthly, the sequence of events in the last episode in Case 1, particularly the rise in temperature from the 7th to the 10th days after ingestion of the incriminated agent, strongly suggests that the mechanism is allergic, and similar to such conditions as the seventh-day rise in temperature not infrequently noted during sulphathiazole treatment, photosensitization by sulphonamides, and second-week penicillin reactions.

It may be that the early generalized papular eruption is precipitated by the unaltered drug, while the epidermolysis seems much more likely to be a response to an allergen, possibly proteose- or protein-conjugated. In Case 2 the mechanism may also be toxo-allergic, sensitization being in some way induced by dapsone taken over a prolonged period, but manifesting itself with dramatic suddenness.

Photosensitization seemed not to play a determinative part: for the nose was spared in the hypermelanosis, and covered and uncovered parts of the limbs were involved indiscriminately.

Parallergic sensitivity is a possibility that cannot be absolutely excluded, but no positive evidence exists for the assumption.

The value of the prednisolone administered is uncertain. In Case 1 it may have reduced the fluid exudation from the denuded surface; in Case 2 it was probably given too late in the course of the disease to have any effect.

In conclusion, the occurrence of a virtually identical syndrome precipitated by two compounds widely different in chemical structure is in keeping with the suggestion (Lyell, 1956; Rook, 1957; *Year Book of Dermatology and Syphilology, 1957–58*) that the characteristic clinical appearances are probably a non-specific cutaneous response to a variety of "toxins" (using the word in its widest sense) causing extensive damage to the suprapapillary zone of the epidermis, in the same manner as fixed drug eruptions or papulo-erythematous rashes may be the limited response-pattern to chemically dissimilar products.

In the 10 reported cases of toxic epidermal necrolysis, phenolphthalein has been suspected twice (Lang and Walker, 1957), penicillin once (Lang and Walker, 1957), and phenylbutazone once (Lyell, 1956). One patient had had aspirin and Dover's powder (Lyell, 1956), and another methyl salicylate application and chenopodium oil by mouth (Lang and Walker, 1956); in the latter case the aperient given is not indicated, but the occurrence of hyperpigmented macules on the trunk and a slate-grey pigmentation of the soles suggests a phenolphthalein-induced fixed eruption similar to the first case here reported.

In view of the widespread use of laxatives and sedatives (barbiturates, ureides) that can be freely purchased, the possibility of further cases of toxic epidermal necrolysis must be recognized. On the evidence now adduced, pre-existing sensitization to such products would seem to be an important—perhaps an essential—factor, and residual sensitivity indicates a predisposition to recurrence of the epidermolysis.

Summary

Two typical cases of "toxic epidermal necrolysis" are reported in which phenolphthalein and dapsone were respectively the causative drugs. Both patients had hypermelanotic fixed eruptions caused by the drugs, and both experienced more than one attack of the syndrome, each attack being apparently precipitated by the agent in question and affecting the skin of all four limbs. The mechanism is apparently allergic.

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A CONTROLLED TRIAL OF "GERIOPTIL"*

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This paper describes a clinical trial of the effect of "gerioptil" on certain psychological dimensions in a group of senile patients. Gerioptil is the trade name of a preparation which contains Professor Anna Aslan's compound H3 together with a variety of vitamins and vitamin derivatives. It is manufactured by a German drug firm, but is available to hospitals and general practitioners in Britain.

H3 is the name given by Professor Aslan, of the Geriatric Institute in Bucharest, to diethylaminoethyl *para*-aminobenzoate, better known as procaine. This substance has been used for half a century or so as a local anaesthetic, and from time to time for other purposes, including coronary and peripheral vascular disease, allergic states, and rheumatoid arthritis, although for these lesser-known uses it has been superseded by other more efficient or more convenient remedies.

During the last few years, however, a number of papers have appeared, many from Professor Aslan and her colleagues (1959) themselves, advocating the use of H3 in a wide group of disorders, including senility and the physical and psychiatric syndromes seen in association with it.

However, much criticism has been levelled at the clinical reports of these workers, whose papers fall below the standards of statistical method, scientific control, and trial procedure which the modern clinician is entitled to expect from workers making the extensive therapeutic claims that have been advanced by this group. The evidence which Aslan puts forward cannot rival her therapeutic optimism; frequently there are impressive clinical reports and anecdotes, but the use of controls and standardized procedures are not apparent. These criticisms have been the subject of a leading article in the *British Medical Journal* (1959a).

Professor Aslan herself delivered a lecture on H3 in November, 1959, and this has also been reported with considerable criticism in the *British Medical Journal* (1959b).

Accordingly, since with this freely available preparation there appeared to be a discrepancy between the therapeutic claims on the one hand and the acceptable evidence of its value on the other, it seemed suitable to make it the subject of a controlled trial.

Design

Six subjects and six controls were selected at random from a group of 12 elderly women with moderate or advanced senile or arteriosclerotic dementia. Mental deterioration in old people is generally considered to show itself in certain ways. Among these are impairment of memory and of simple learning abilities, impairment of the ability to perceive and reproduce simple visual patterns accurately, and impairment of intellectual capacities. In contrast, vocabulary is not considered to deteriorate so markedly, and can serve to provide an estimate of premorbid intelligence level.

Selected indices of the above abilities were estimated before the trial. Then the subjects were given first 0.5 ml. of 2% procaine subcutaneously, then 2 ml. of 2% procaine intramuscularly, to obviate the possibility of procaine sensitivity; this was followed by a course of 12 injections of gerioptil H3 intramuscularly over the course of a month as advocated by the makers. The controls were given similar injections of sterile water.

The patients were then reassessed, using the same or parallel test procedures. The test administrator did not know at this stage which patients were members of the experimental group and which of the control group.

Test Procedure

To assess memory and simple learning abilities the two parallel test forms of the Wechsler memory scale were used (Wechsler, 1945; Stone *et al.*, 1946). These forms each contain seven subtests which cover questions on personal and current information, orientation, and other long-term routine memory items; also several simple short-term learning tasks or tests of memory for the immediate past, using numbers, stories, and also simple diagrams and word associations. The form administered first to any patient was determined by chance, using a list of random numbers. The alternative form was then used later for reassessment. The rules for scoring as well as for administration of every item in these tests are quite specific and precise. Improvement or deterioration in memory and learning ability was determined by comparison of raw scores and subtests. On the full scales the total score is corrected for age by the addition of an appropriate constant to give a so-called memory quotient, but differences in total raw scores and differences in memory quotient are obviously the same.

The Bender gestalt test of figure-drawing (Bender, 1938) was used to assess ability to perceive and reproduce simple visual patterns. No time limit is involved, and all that is required is to copy a few apparently simple geometric figures. With any one of these, however, certain key theoretical components of sensorimotor organization must be in operation, otherwise there is a tendency for the figure to be changed and reorganized in the drawing. Impairment of ability or immaturity of development can be identified from the drawing produced, which may be given a mental-age score. There are no parallel forms for this test, and the same figures were therefore used for retesting.

Intellectual capacity was tested by the simpler coloured version of Raven's (1956) Progressive Matrices, using the norms he has published for old people (Raven, 1958a). Ability on this test is severely diminished in senile dementia. For retesting, the identical test was used again, as no parallel form exists.

Finally, to estimate premorbid intelligence level, the Mill Hill vocabulary definitions scale was used. Two equivalent lists of words are contained in the full test, and these were used separately as parallel forms, the scores obtained on each occasion being pro-rated to obtain the total score. Raven's (1958b) norms for old people on this test explicitly contrast and compare it in detail with his coloured progressive matrices.

*Based on a paper read at a meeting of the Manchester Regional Psychiatric Association at Lancaster Moor Hospital on June 29, 1960.

Results

After retesting, raw scores were compared on each test and subtest, and each patient was placed in one of three categories, "improved," "no change," or "deteriorated," for that particular function. On the complete battery of tests, including the Mill Hill vocabulary definitions scale, each patient was also given an overall rating signifying change in one direction or the other.

According to the claims made for gerioptil, the hypothesis expected to be supported by the results is that all those patients who were treated with this preparation would improve, while those who did not receive it would continue to deteriorate in accordance with the natural course of the disease, as in Table I, Hypothesis I.

Allowing for the effects of extraneous factors, it would still be supposed that those treated with gerioptil would show an improvement as a group when compared with those not so treated; such a modification of the basic hypothesis is shown in Table I, Hypothesis II. Moreover, since the claims made for gerioptil are quite extensive, not only an overall improvement would be expected, but also an improvement in each mental function assessed, or at least in one or two of them.

Such hypotheses, however, are not compatible with the results. Overall, four out of six patients who had treatment deteriorated, while five out of six untreated patients improved; these results are shown in Table I. Also in Table I are the results for each separate test, and these show that there was no improvement in any one of the mental functions assessed. The results for individuals are shown in Table II.

The memory of all the subjects treated with gerioptil and the intellectual capacity of half of them deteriorated; and this was the pattern of the findings throughout all seven subtests of the memory scale, with the exception of only one. This exception was memory for design, in which the experimental group showed a slightly greater improvement than the control. In one other, personal and current information, subjects tied with controls; while in the remaining five, orientation, mental control, logical memory for stories, digit span, and associate learning, the results in the control group were more favourable by comparison. In the Bender gestalt figure-drawing test, although the results were not so markedly against gerioptil, they still provided no evidence in its favour.

Even the Mill Hill vocabulary definitions scale weighs against gerioptil, although assessing a mental capacity supposedly less affected by dementia than are the other psychological indices. On this test, four out of six patients who received gerioptil did not score so highly on the second occasion, whereas four out of six patients who did not receive the treatment improved in their scores.

TABLE I

	Overall Changes		Memory		Figure Drawing		Intellectual Capacity		Vocabulary		Hypothesis I		Hypothesis II	
	G	P	G	P	G	P	G	P	G	P	G	P	G	P
Improved	1	5	0	4	3	4	2	3	2	4	6	0	3	1
No change	1	0	0	1	1	0	1	2	0	1	0	0	2	2
Deteriorated ..	4	1	6	1	2	2	3	1	4	1	0	6	1	3

G=Gerioptil. P=Placebo.

TABLE II

Patient	Age	Memory Scale Raw Scores		Mean Figure Drawing Age Levels (in Years)		Coloured Progressive Matrices Scores		Mill Hill Vocabulary Scores		Overall Trend
		I	F	I	F	I	F	I	F	
Gerioptil Group										
A	64	4	0	3	4	0	0	14	0	−
B	76	9	6	3	4	14	0	33	22	−
C	75	19	11	5	4	7	6	45	39	−
D	81	15	5	3	4	11	9	53	58	0
E	75	41	37	8½	8	14	19	63	62	−
F	75	42	35	8	8	23	27	53	57	+
Control Group										
G	79	25	14	4½	6	12	14	39	42	+
H	76	30	43	8	7½	18	23	44	44	+
I	73	0	7	3	5	13	13	42	48	+
J	84	12	12	7	6	14	9	42	45	−
K	79	0	8	3	4	7	7	27	26	+
L	71	8	16	3	5	7	11	36	49	+

I=Initial. F=Final. +=Improved. 0=No change. −=Deteriorated.

Conclusions and Discussion

Although the numbers concerned have been far too small for statistical computation, nevertheless the results suggest quite clearly that those patients who did not receive the course of treatment had the natural progression of their disease retarded to some extent, while those who were treated with gerioptil deteriorated still further. In fact, an effect contrary to the claims made for gerioptil seemed to have occurred, and this trend is reflected in almost every part of each test taken separately.

Both subjects and controls had other treatment in the form of sedatives, hypnotics, and tranquillizers during the trial, but, whereas this was necessary for their own welfare and comfort, it should not be expected to interfere with any effect on the intellectual dimensions under review; nor was any treatment given which is listed as contraindicated during gerioptil therapy by the makers.

The limitation in the number of subjects in the trial was necessary in view of the very laborious and time-consuming nature of these psychological estimations in demented patients, since one of us (T. G. G. L.) had to spend in all something of the order of six to seven hours with each patient, while continuing other research work and routine clinical work as well. This points to the possibility of increasing the number of subjects and controls but limiting the extent of the formal intellectual assessment in a future trial.

The reliabilities and validities of some of the tests used in this study have been called in question. Hall (1957), for example, examined the reliabilities and correlations with intelligence of the Wechsler memory scales, using a group of young adult, non-organic, psychiatric patients. She found the internal consistency of the subtests generally low, and their correlations with intelligence high, so that she queried the uniqueness of the contribution the Wechsler memory scale could give to studies of human behaviour. Wechsler (1960) has emphasized that neither of his memory scales has been very thoroughly standardized, and that they were intended primarily as clinical instruments. Inglis *et al.* (1956) concluded that memory function was not particularly useful in the differential diagnosis between elderly psychiatric patients having disorders of functional and organic origin respectively. On the basis of their results they suggest that the Bender gestalt test gives a more valid contribution to the required criterion. On the other hand, their evidence does point to the existence in their patients (after the influence of intelligence on the subtests has been computed and removed by the technique of partial correlation) of some such thing as "memory function."

Notwithstanding these remarks, in the absence of any other data, the results obtained in this trial cast very grave doubts upon the claims made for the preparation used.

Summary

A small controlled trial has been carried out with six subjects and six controls of the effect of "gerioptil H3" on the mental ability, as measured by a number of psychological tests, of patients with senile or arteriosclerotic dementia. The trial has failed to prove that gerioptil is of any value in this respect.

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RESPIRATORY PARALYSIS AFTER A LARGE DOSE OF STREPTOMYCIN

REPORT OF A CASE

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A number of cases have been reported in which intraperitoneal administration of neomycin in large dosage has been followed by the development of post-operative respiratory insufficiency or apnoea (Pridgen, 1956; Poth, 1957; Middleton *et al.*, 1957; Engel and Denson, 1957; Ferrara and Phillips, 1957). Streptomycin has been shown to be capable of blocking neuromuscular conduction in experimental animals (Brazil and Corrado, 1957; Bezzi and Gessa, 1959), and in human intercostal nerve–muscle preparations (Sabawala and Dillon, 1959). Loder and Walker (1959) have reported three cases of muscular weakness and visual difficulty, resembling a myasthenic state, in patients receiving standard intramuscular doses of streptomycin. The symptoms were relieved by neostigmine and by withdrawing the streptomycin.

Streptomycin is not infrequently instilled into the peritoneal or pleural cavity at the end of some surgical procedures, and Bush (1961) has described the occurrence of prolonged post-operative apnoea in a child aged 6 months, which he attributes to neuromuscular blockade by the combination of D-tubocurarine and a large dose of streptomycin (1 g. intraperitoneally). I feel that a similar case occurring in an adult is worth reporting.

Case Report

The patient, a fit man aged 53, had a stricture of the lower end of his oesophagus. An oesophageal hiatus hernia had been repaired nine weeks previously, when he was noted to be somewhat resistant to anaesthetic drugs. His weight was 12 st. (76.2 kg.), haemoglobin 13.8 g./100 ml., and blood pressure 135/80 mm. Hg; he was classed as a good risk for anaesthesia and surgery. The proposed operation was an ileocaecal transplant and anastomosis for relief of the oesophageal stricture.

Premedication with papaveretum 20 mg. and scopolamine 0.4 mg. was given at 8 a.m. At 9 a.m. thiopentone 0.4 g. and then suxamethonium 50 mg. were given intravenously, the lungs were inflated with oxygen, and 2 ml. of 5% cocaine solution was instilled into the trachea, followed by intubation with a No. 10 cuffed Magill tube.

Operative Course

When the ileocaecal transplant had been mobilized and anastomosis with the oesophagus started, its blood supply was found to be inadequate. The ileocaecal transplant was therefore resected and replaced by jejunum, the whole procedure lasting seven hours. The patient was resistant to the drugs used, and a total of 87 mg. of D-tubocurarine and 170 mg. of pethidine, and a further 0.2 g. of thiopentone, were required to control "bucking" and straining. He was ventilated throughout with nitrous oxide and oxygen, by the Bleese pulmoflator or by hand through a Waters canister. The blood-pressure was steady at about 110 mm. Hg systolic except for a short period when it fell to 90 mm. Hg, when 9 mg. of methylamphetamine was given. The blood loss, measured by weighing the swabs and adding to the loss via suction, was 1,030 ml., and 1,500 ml. of whole blood was replaced together with 1 g. of calcium gluconate. Before the wound was closed a total of 10 g. of streptomycin powder was administered, 5 g. being placed in the peritoneal and 5 g. in the pleural cavity. Spontaneous respiratory movements began during closure, after which atropine 1.2 mg. and then neostigmine 2.5 mg. were given intravenously. The patient left the theatre at 4 p.m., when his general condition was satisfactory, his blood-pressure being 110 mm. Hg systolic, and respiratory function appeared adequate.

On the way back to the ward, respiratory movements diminished greatly over a period of two to three minutes, becoming very shallow. The patient was rapidly returned to the theatre, reintubated, and ventilated with oxygen. The state of his circulation was quite satisfactory at this time. blood-pressure being unaltered. Atropine 0.6 mg. intravenously, followed by two doses of 1.25 mg. of neostigmine, resulted in a marked improvement in spontaneous ventilation, which lasted for less than a minute on each occasion. 2 ml. of nikethamide had no effect. At this stage the blood-pressure fell abruptly and became unrecordable. Intravenous methylamphetamine 30 mg. brought the pressure up to 70 mm. Hg. Additional blood was transfused and hydrocortisone 100 mg. given intravenously. Soon after this the blood-pressure was 120 mm. Hg and his cardiovascular state caused no further anxiety.

Respiratory movements were still very feeble, and the patient was therefore connected to a Barnet ventilator and inflated with oxygen. After a few minutes, assistance by means of the patient-triggering device was sufficient. This was necessary for another hour, during which he became responsive to commands to move his eyelids and head. Towards the end of this time he was able to open his eyes and wrinkle his forehead. At this stage the ventilator was disconnected and he breathed air through the endotracheal tube with no cyanosis, although there was still some tracheal tug and mild ptosis with a "myasthenic facies." Forty minutes later the endotracheal tube was removed. Ventilation was adequate, with only slight tracheal tug and facial weakness. The patient now complained of pain from the incision, and papaveretum 10 mg. was given subcutaneously, with some relief of pain but no adverse respiratory effect. He was finally returned to the ward in a satisfactory condition at 6.30 p.m., and made an uneventful recovery, having no recollection of the events in the immediate post-operative period. However, for some days afterwards he was subject to undefined frightening dreams, and said that he felt a little afraid of falling asleep in case he did not wake up.

Discussion

Initial studies by Molitor *et al.* (1946) on the acute toxicity of streptomycin in animals showed that respiratory depression was the main acute effect of a large overdose and the cause of death in fatal dosage. They showed that artificial ventilation enabled animals to survive an otherwise fatal dose, and that in much larger doses still there was a severe fall in blood-pressure.

Brazil and Corrado (1957) demonstrated a neuromuscular blocking effect of streptomycin, suggesting that this was the cause of the respiratory depression from toxic doses. They found that the block resembled that due to magnesium ions rather than that due to D-tubocurarine, in that post-tetanic facilitation was initially maximal and the block was more fully reversed by calcium ions than by neostigmine, though both were effective.

Bezzi and Gessa (1959) noted an increased susceptibility to D-tubocurarine of patients receiving large doses of some antibiotics, and showed that streptomycin could potentiate the effect of D-tubocurarine in rabbits.

Sabawala and Dillon (1959) demonstrated the neuromuscular blocking action of streptomycin in preparations of human intercostal muscle. They found that it was antagonized by neostigmine, and was about three-tenths as potent as neomycin.

Neuromuscular blockade by streptomycin in the absence of other factors seems to be rare (Loder and Walker, 1959). Bush (1961) suggests that in his case the combination of a very large dose of streptomycin with the use of a non-depolarizing relaxant was responsible for a prolonged neuromuscular block. In the present case the combination of a very large dose of both D-tubocurarine (87 mg.) and streptomycin (10 g.) could have caused the respiratory insufficiency. It is realized that recurarization may have occurred under these conditions without the aid of streptomycin, although the fact that spontaneous respiration was present before neostigmine was administered would suggest that this was unlikely. In view of the work of Brazil and Corrado, perhaps further intravenous doses of calcium gluconate may have been indicated.

In the reports of respiratory depression after large doses (5 to 10 g.) of intraperitoneal neomycin, patients who had been breathing adequately when closure of the abdomen was started became apnoeic some 15 to 20 minutes later. In this case it was some 30 to 40 minutes after the streptomycin was instilled that the effect was noted. The later fall in blood-pressure could have been a toxic effect of a very large dose of streptomycin (Molitor *et al.*, 1946), although the changes in ventilation and drugs used at the time are also possible factors.

Introduction of a large dose of streptomycin into the pleural or peritoneal cavity carries the theoretical risk of increasing neuromuscular block when muscle relaxants are being used. Although the part played by streptomycin cannot be proved in the present case, it is felt that the circumstances strongly suggest a practical as well as a theoretical hazard.

Summary

A case is described of post-operative respiratory insufficiency in which a very large dose of streptomycin had been introduced into the body cavities after a large dose of D-tubocurarine given during the course of an operation lasting seven hours. The pharmacological evidence for a neuromuscular blocking action of streptomycin is reviewed and it is suggested this action was responsible for the complication described.

My thanks are due to Dr. A. M. Hutton, consultant anaesthetist to Guy's Hospital, for his advice and criticism in the preparation of this paper, and to Mr. Robert Brain, consultant surgeon to Guy's Hospital, for permission to publish details of a patient under his care.

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Medical Memoranda

Prolonged Neuromuscular Block Due to Intraperitoneal Streptomycin

Neuromuscular block of a non-depolarizing type has been produced in animals by certain antibiotics. Neomycin (Pittinger and Long, 1958), streptomycin (Vital Brazil and Corrado, 1957), and polymyxin B (Sabawala and Dillon, 1959) have been shown to have a blocking action on the muscle end-plate. A similar effect has been described in humans after the intraperitoneal instillation of neomycin (Pittinger and Long, 1958) and the parenteral injection of streptomycin (Loder and Walker, 1959).

In the following case a persistent neuromuscular block was believed to have been due to intraperitoneal streptomycin sulphate.

CASE HISTORY

A male infant aged 6 months and weighing 13 lb. (5.9 kg.) was presented for rectosigmoidectomy for Hirschsprung's disease. Since a transverse colostomy at the age of 2 weeks the baby had thrived.

Atropine sulphate, 0.3 mg., was given at 9.30 a.m., and anaesthesia was induced at 10.30 a.m. with thiopentone sodium, 20 mg., followed by D-tubocurarine chloride, 4 mg., given into an intravenous infusion. Intubation was performed with a size 0 Magill orotracheal tube, and anaesthesia was maintained with N_2O and O_2, 4 and 3 litres a minute respectively, with controlled ventilation given by Rees's (1959) modification of Ayre's T-piece. The operative procedure consisted of a hemicolectomy and lasted four hours, during which another 4 mg. of D-tubocurarine chloride, given in divided doses, was required to secure adequate control of respiration; the last 1 mg. was given one and a half hours before the end of the operation. Blood loss was 66 ml., and 110 ml. of blood was given during the surgical procedure. Spontaneous respiration was resumed 45 minutes before the end of the operation, but with the aid of continued hyperventilation relaxation was deemed to be adequate to permit closure of the abdomen.

Streptomycin sulphate was instilled into the peritoneal cavity; inadvertently 1 g. was administered. It was noticed that the relaxation became more complete and attempts at spontaneous respiration ceased. The possible significance of this was not appreciated at the time. Atropine sulphate, 0.12 mg., was given intravenously at 2.30 p.m., and with the resumption of spontaneous respiration 0.5 mg. of

neostigmine sulphate was given intravenously at 2.35 p.m.; this produced a small increase in the depth of respirations, though ventilation was obviously grossly inadequate. The patient's general condition gave no cause for concern. At 2.40 p.m. the child was covered with a blanket and taken into the anaesthetic room, and controlled ventilation was continued. His axillary temperature at this time was 96.3° F. (35.7° C.). Neostigmine sulphate, 0.25 mg. intravenously at 2.45 p.m., again produced a slight improvement. At this stage there was a marked tracheal tug, and, although the child would half open his eyes, the limbs were completely atonic and there were no spontaneous movements. Hyperventilation was reinstituted in case there was a respiratory acidosis, but this produced no improvement. Controlled ventilation was therefore continued for the next two hours. At 4.45 p.m. a venous sample of blood showed: *p*H 7.35–7.4, alkali reserve 18 mEq, and pCO_2 33. The possibility of a streptomycin-induced neuromuscular block was then considered, and, acting upon this suggestion, the following treatment was given.

Edrophonium, 1 mg. intravenously at 5 p.m., produced a noticeable improvement in the depth of spontaneous respiration, and movements of the fingers appeared for the first time. At 5.30 p.m. atropine sulphate, 0.12 mg., followed by neostigmine sulphate, 0.5 mg., was given intravenously. This produced marked improvement, and the endotracheal tube was removed as the respirations were judged to be adequate. Limb movements were also present but incoordinate.

During the next four hours the child was kept under close supervision in the anaesthetic room. The condition gradually improved, with limb tone becoming normal. Muscular incoordination typical of a mild neuromuscular block was still in evidence some 10 hours after the completion of the operation, though the general condition was satisfactory.

During the post-operative period the child developed a mild respiratory infection, which responded well to parenteral penicillin. Subsequent convalescence proceeded satisfactorily.

DISCUSSION

Despite the fact that it was not possible to demonstrate conclusively that this child was suffering from a persistent neuromuscular block, the clinical state was typical of this condition. The total dose of D-tubocurarine chloride was 8 mg., which is not excessive for a child of this age, bearing in mind the length of the operation. Attempts at spontaneous respiration occurring 45 minutes before the termination of the surgical procedure strongly suggested that the persistent block was not due to hypersensitivity to D-tubocurarine. Of even greater significance was the increase in relaxation and abolition of attempts at spontaneous respiration that occurred soon after the instillation of streptomycin sulphate into the peritoneal cavity.

Potentiation of the action of D-tubocurarine by carbon dioxide excess, as demonstrated by Payne (1958), is not likely in this case, since hyperventilation did not improve the condition, and the biochemical findings do not conform to those found in respiratory acidosis.

To date streptomycin has not been implicated in inducing a paralytic state during anaesthesia, though it has been shown that patients receiving streptomycin parenterally for infective conditions can develop weakness of voluntary muscles, particularly the eye muscles, which can be dramatically reversed by neostigmine therapy (Loder and Walker, 1959).

In dogs Vital Brazil and Corrado (1957) showed that streptomycin given intravenously in a dose of 110 mg./kg. will produce complete neuromuscular block. This child received a dose of 169 mg. of streptomycin sulphate per kg. intraperitoneally. It is known that considerable amounts of antibiotics are rapidly absorbed into the circulation after administration into the peritoneal cavity (Schatten and Abbott, 1958). As the dog is more resistant to D-tubocurarine than the human (Zaimis, 1958), it would appear that the dose given in the present case was well within the range of that required to produce neuromuscular block.

The neuromuscular blocking action of the antibiotics neomycin and streptomycin is usually produced only when another drug is used which exerts a similar action at the motor end-plate. Such a combination may occur during ether anaesthesia (Pittinger and Long, 1958), during anaesthesia using a depolarizing relaxant (Middleton *et al.*, 1957), if prolonged administration of the relaxant has changed the sensitivity of the end-plate to depolarizing influences, or during anaesthesia using non-depolarizing relaxants (Foldes, 1959).

The need for immediate, effective, and, if necessary, prolonged controlled ventilation in cases of prolonged neuromuscular block due to antibiotics has been stressed (Sabawala and Dillon, 1959). The value of continued adequate ventilation is well shown by this case, which had a happy outcome. Neostigmine has been shown to reverse the neuromuscular blocking action of streptomycin (Vital Brazil and Corrado, 1957; Sabawala and Dillon, 1959; Loder and Walker, 1959). Similarly in this case neostigmine in the dose used exerted a noticeable antagonistic action to the neuromuscular block. To obtain maximum benefit from neostigmine, it should be administered only when there is evidence of a reduction in the intensity of the block and when spontaneous respiration is present. The dose of neostigmine, which should be preceded by atropine, should not exceed 0.08 mg./kg. Neostigmine must not, however, be relied upon to produce adequate ventilation, and whenever there is doubt about the adequacy of the tidal volume controlled ventilation should be continued for as long as is necessary.

In view of the probable aetiology of the prolonged neuromuscular block in this case, it is interesting to speculate whether any of the numerous cases of "neostigmine-resistant curarization," as originally described by Hunter (1956), could have been due to the neuromuscular blocking action of intraperitoneally administered streptomycin. Since this condition is preventable, care should be taken that only the correct dose of these potentially dangerous drugs is administered intraperitoneally or indeed intrapleurally.

My thanks are due to Dr. A. L. Stead for help and encouragement during the preparation of this paper, and to Dr. G. Jackson Rees and Professor T. Cecil Gray for their advice and stimulating interest. I am grateful to Mr. P. P. Rickham for permission to publish this case.

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Reviews

COMMISSIONING A HOSPITAL

Commissioning a New Hospital. An Interim Report by J. A. Oddie, M.B., B.S., and the Swindon and District Hospital Management Committee. (Pp. 261+iv. 10s. 6d.) Oxford: Oxford Regional Hospital Board, 43 Banbury Road. 1961.

This is a book of great topical importance. For the first time within living memory hospital building is starting on a large scale, and many hundreds of doctors and administrators are actively concerned with planning new hospitals. For each and all of them *Commissioning a New Hospital* is essential reading.

The Princess Margaret Hospital at Swindon is the first of the new English hospitals to come off the production line. Its shape has largely been determined by the valuable researches of the Nuffield Division of Advanced Architecture and the Nuffield Provincial Hospitals Trust. The idea that the commissioning of a new hospital should be studied and recorded in detail was put forward to the Oxford Regional Hospital Board by the Nuffield Provincial Hospitals Trust in 1957. Fortunately the secretary of the Trust, Mr. Gordon McLachlan, had served in the Royal Navy. He seized on the analogy between the commissioning of a ship, under a prescribed plan of action built up by years of study and experience, and the creation of an efficient hospital in full working order. Equally fortunately, his suggestions fell on receptive ears at the Board. A working party was created, and Dr. J. A. Oddie, the Deputy S.A.M.O. of the Oxford Region, became chairman of what was called the Swindon Planning Committee. At first the committee spent a day a week on its activities; then, after a year, a day a fortnight. The results of its work are here set out in detail for the benefit of all who have to tread the same road. The value of having a senior medical administrator as officer commanding the operation is everywhere apparent. The creation of a new hospital is a major social and industrial task, needing both wisdom and technical skill. The Planning Committee commanded both.

If our method of hospital building by what Sir George Schuster in his foreword describes as "decentralized empiricism" is to succeed, it is essential that we should all be prepared to chronicle both our successes and our mistakes, so that others may profit from them. This is precisely what the report does, with a degree of integrity which all must respect. It is a remarkable tribute to the architects, Messrs. Powell and Moya and Mr. Llewelyn Davies, that only three errors of substance appear to have been made. The first is the failure to provide the casualty department with its own *x*-ray unit. The second is the inadequate provision of "intermediate" waiting-space at the points of treatment. The third is the window design, and the excessive use of glass, especially in rooms requiring privacy. An illuminating photograph appeared in the *Daily Telegraph* of January 31, 1961, showing the view into a consulting-room from the top of a double-decker bus in the road adjacent to the hospital.

Glass curtain walling can contribute much to cheerful brightness in corridors, waiting-spaces, and living-rooms. But even here it produces severe problems of heat conservation and ventilation. For rooms where patients have to be seen, and doctors have to work, where ventilation with ordinary fresh air may be desirable at a moment's notice, smaller windows are essential. The manipulation of large glass swinging panels has proved difficult for the staff, and where a part of the window swings inwards there are always problems with curtains and blinds, particularly if a full black-out is sometimes needed. Of the pivoted windows so far inspected, the best we have seen is that specially designed for the Nuffield health centre buildings near the town centre at Harlow. But the conventional E.J.M.A. window, with a small hopper panel and two side-hung main panes as used domestically, is in our experience still really the best.

Space heating, flooring, sound insulation, and the protection of walls from splashes have all presented their special problems, to which there are as yet no universal panaceas. But the present report gives some valuable hints. It is a further tribute to the skill of the architects that the total number of variation orders requested by the Planning Committee and approved was only 93 items, costing £7,833.

In one respect this report is incomplete. Since it is concerned with commissioning and not with initial planning, it does not give those detailed studies of population projection, morbidity rates, and probable work-loads which are an essential prerequisite to planning a hospital. No doubt the Nuffield Trust will once again put us in its debt by well-timed stimulation of another hospital board which is starting its job at the very beginning. Nevertheless, the great importance of the proper briefing of the architect in advance by the users, and the preparation of detailed schedules of accommodation, is rightly stressed. Indeed, if the advance paper work is done really thoroughly by the administrators, medical and lay, *before* the architects come into the picture, the overall success of the ultimate plan can be assured. We look forward with keen anticipation to a similar report on the commissioning of the further stages of the hospital.

TAYLOR.

OCCUPATIONAL HEALTH

Modern Trends in Occupational Health. Edited by R. S. F. Schilling, M.D., M.R.C.P., D.P.H., D.I.H. (Pp. 313+ix; illustrated. 67s. 6d.) London: Butterworth and Co. (Publishers) Ltd. 1960.

This is one of the most important books on occupational health that has been published in Great Britain. Some 300 pages contain a remarkable amount and wide range of up-to-date information provided by 25 contributors. Both they and their subjects have been selected well. The main credit for this ever-difficult matter must go to the editor, Professor R. S. F. Schilling, whose opening chapter on the measurement of health sets the high standard of exposition which is maintained throughout. It is interesting to note that only three or four of the authors are apparently engaged in the general practice of industrial medicine; the others are mainly research workers and university teachers. This itself is a significant trend. During the past ten years there has been an increasing appreciation of the need for more scientific investigation of the effects of occupation on health. Money has become available for this purpose and so investigators of quality have now entered the field, working for the Medical Research Council or on the staff of university departments, as well as within industry itself. This has had an invigorating impact on occupational health which was sorely needed in its post-war development.

It may be held by the reader that toxicity testing, the measurement of lung function, pesticides, occupational cancer, or radiation hazards are rarely the concern of the industrial medical officer in his daily work. But at any time he may have good reason to seek information about them, and here it is. A clear demonstration of the widening of the horizon of occupational health beyond that of the purely medical approach is the inclusion of subjects reviewed and discussed by non-medical writers. These include accident prevention, vocational psychology, morale and the working group, ageing and employment, machine design and human engineering, and industrial law. Few, if any, of these subjects could be covered as adequately by practising industrial physicians. Although we are told that more than a thousand papers on industrial pulmonary disease have been published in the last five years, a concise review of this subject has been wisely provided. Of much practical value are the chapters on noise, the teaching of occupational health, medical services in small factories, mental illness and work, routine medical examinations, the toxicology of metals, and the treatment of industrial injuries. The variety of subjects in the book, their importance, the standard of presentation, and the generous lists of references, make it certain that no person seriously working in this field can afford to be without it.

DONALD STEWART.

TROPICAL DISEASES HANDBOOK

Clinical Tropical Diseases. By A. R. D. Adams and B. G. Maegraith. Second edition (Pp. 540+x; illustrated. 52s. 6d.) Oxford: Blackwell Scientific Publications. 1960.

In 1953 the authors of this work set out to produce an up-to-date handbook on the clinical diagnosis and treatment of diseases occurring primarily in the tropics. They omitted detailed descriptions of organisms causing disease and of their vectors; they made no attempt to be encyclopaedic in their scope. The success which all reviewers of the first edition predicted has been achieved, and the wide adoption of this book in schools all over the world has been well deserved. The second edition includes all important advances made in the past seven years.

The sight of patients lying in bed for hours trying to retain chiniofon enemata has led the reviewer and most other tropical physicians to abandon such therapy in amoebic dysentery. We have altogether too many colon-conscious patients, but the Liverpool school still seems to find some virtue in such methods. More detailed guidance is needed in the treatment of amoebic liver abscess. Most large abscesses have to be aspirated even if pyrexia is reduced and symptoms abate with a course of emetine followed by chloroquine for a fortnight. The value of intraneural injections of hydrocortisone, hyalase, and procaine in the neuritis of leprosy is worthy of mention; the use of steroids in the prevention of further haemolysis in blackwater fever is now generally accepted. In outbreaks of cholera we find rows of patients in the streets and under trees and on railway platforms. Transfusion fluids must be boiled till sterile, but insistence on pyrogen-free water is unrealistic; outside hospital wards estimation of the specific gravity of the blood is not used in epidemic conditions. In acute cholera it is rare to be able to transfuse without cutting down on the vein. The importance of adding potassium to the transfusion fluid to make up for the heavy losses will doubtless be emphasized in the next edition.

The alphabetical arrangement of diseases from A to Y (Ainhum to Yaws) enables one to look up a particular disease quickly. This handbook is not intended to supersede the classic Manson, but in its own field is unsurpassed.

GEORGE R. MCROBERT.

MEDICAL ANNUAL

The Medical Annual. A Year Book of Treatment and Practitioners' Index. Edited by R. Bodley Scott, M.A., D.M., F.R.C.P., and R. Milnes Walker, M.S.(Lond.), F.R.C.S. 78th Year. (Pp 572; illustrated. 42s.) Bristol: John Wright and Sons, Ltd. 1960.

Most medical men believe that they are, on the average, far busier than their predecessors in days gone by. While this may or may not be the case, there can be no doubt that they have far more to read. The vast number of journals and the writing of papers of which there is no end have made it impossible for even the most diligent doctor to keep himself familiar with the literature even in the small corner of medicine in which he may happen to be particularly interested—much less with the whole range of the clinical sciences. Already most of us have come to rely on abstracts, annual reviews, and articles on recent advances to keep ourselves conversant with the aspects of medicine outside our immediate purview. It may well be that in the future original articles will be read largely by specialists and that ordinary doctors will be vicariously nourished by their ruminations.

The *Medical Annual* has for many years been the leading British review of medical and surgical progress, and the 1960 edition has more than maintained the reputation of its seventy-seven predecessors. There are 44 distinguished reviewers who have made critical clinical abstracts of the more important papers published in recent years, and in some cases have written special articles on them. The review covers not only medicine, surgery, and paediatrics, but gynaecology and obstetrics, ophthalmology, dermatology, radiotherapy, and anaesthesia as well. It is all very well done and the volume is not unduly expensive.

DERRICK DUNLOP.

THE FIRST MONTH

Diseases of the Newborn. By Alexander J. Schaffer, M.D. Section on Neonatal Cardiology by Milton Markowitz, M.D. (Pp. 878+xv; illustrated. £7.) Philadelphia and London: W. B. Saunders Company. 1960.

This is a very large book to be entirely devoted to the diseases of the first month of life. It is a remarkable effort to be the work of one author, and no disease seems to have been left out. The approach to the subject is orthodox. After a section on the normal and abnormal newborn infant the various systems—respiratory, cardiovascular, gastro-intestinal, and so forth—are each considered in separate sections. The skin and the eye are accorded sections of their own. There are also individual sections on such important problems as infection and jaundice in the neonatal period. The book finishes with four useful appendices on the principles of infant care in nurseries for the newborn, resuscitation in the labour room, the treatment of erythroblastosis, and a pharmacopoeia for the newborn period. Some of the recent work on the physiology of the newborn is rather briefly considered in some sections, but a more detailed account in a separate section would have been welcome to paediatricians. British paediatricians will find in this book little that is strange or with which they

would disagree. Many, however, will find that the words "neonatology" and "neonatologist" strike harshly on their ears.

The book is beautifully produced, though heavy to hold, and the illustrations and line drawings are particularly good. This type of book, which gives detailed descriptions of the common and the rare, will be popular with the American family paediatrician, for it will give him practical and detailed information about every problem he is likely to meet in the newborn. Its high cost is unlikely to commend it to the British general practitioner. It will be a useful addition to medical libraries, especially in children's hospitals, and hospital paediatricians engaged in consulting practice would find a personal copy a valuable source of quick reference. The references in each section have been well chosen, and it is pleasant to find in an American textbook that British work has received full recognition.

J. H. HUTCHISON.

HOMICIDE, SUICIDE, AND MENTAL ILLNESS IN AFRICA

African Homicide and Suicide. Edited by Paul Bohannan. (Pp. 270+xix 48s.) Princeton, N.J.: Princeton University Press. London: Oxford University Press. 1960.

Search for Security. An Ethno-psychiatric Study of Rural Ghana. By M. J. Field. (Pp. 478. 42s.) London: Faber and Faber. 1960.

The editor of *African Homicide and Suicide*, a former Rhodes Scholar and lecturer in social anthropology at Oxford, has, together with six associates, carried out field studies of homicide and suicide in Nigeria, Uganda, and Kenya. They had access to the files of the British police and judicial courts responsible for the administration of the law among seven tribes. Several types of homicide were found: accidental non-culpable; ritual, which was rare; and killing for theft, adultery, and in self-defence. Among the motives, adultery of the wife and land disputes were the most common. Many murders were committed under the influence of drink. A considerable proportion of the murderers were found to be mentally ill. The authors emphasize the importance of viewing homicide in its social setting, with special consideration of the relationship between killer and victim. Homicide rates among African negroes were far below those of American negroes. They were even lower than among the general population of the United States and did not exceed the European rates.

Information about suicide was more difficult to come by, and the incidence figures varied considerably in different tribes. In some the suicide rates reached those of Western communities. Adultery, impotence, childlessness, loss of status, and desire for revenge were common motives. Polygamy was frequently responsible for fatal conflicts. Hanging was the most common method used. Suicide is believed to cause a state of ritual uncleanliness and danger, which must be purged by burning down the house in which it happened or the tree which was used for hanging, etc. Malevolent supernatural forces are supposed to be released by suicide. This is why the tribal community condemns and dreads suicide, and why the suicidal threat sometimes achieves what otherwise cannot be gained. The role of mental illness in the causation of suicide could not be considered, but it must have played at least as important a part as in homicide.

European influence did not appear to have had a consistent effect on the homicide and suicide rates. The authors formed the impression that tribal Africa, in spite of the social disturbances due to the Western impact, is still a rather stable community in which strife is relatively well controlled. This book is an important contribution not only to the study of tribal Africa, but also to the knowledge of homicide and suicide in general.

The author of the book on rural Ghana is a medically qualified anthropologist with psychiatric training. She reports on observations made by her from the vantage point of shrines for relief from witchcraft and kindred ills. The first part of the book deals with the patients' social, economic, and ideological background, their ideas of spirit possession, and their various day-to-day tribulations. Many of those seeking help at the shrines also professed Christian beliefs. Two-thirds of the book are taken up by the case reports of 146 patients. Like other students of mental illness among Africans, Dr. Field observed the same basic types of disorders as seen in Europe. Unlike earlier observers, she found depressive illness fairly common. She is of the opinion that if it was not for the delusional self-accusations of depressed patients the idea of witchcraft would have died out long ago. Hysterical dissociation tends to be experienced as a state of devil possession. There is an interesting chapter on the similarities between the spirit possession experienced among the Ashantis and states reported by the ancient Hebrew prophets. Mental illness, according to Dr. Field, plays an important part in the preservation of the primitive ideology of the general population, of which the mentally ill form an integral part. This theory is not incompatible with the one held in Western society according to which the mentally ill regress to more primitive modes of behaviour and thinking.

It is difficult to assess how representative of the mentally ill the patients observed by Dr. Field were. Are those shrines comparable to our out-patient clinics, or to places of pilgrimage such as Lourdes? Probably they are the Ghanaian equivalents of both. It is noteworthy that none of the patients seen by the author was known to have committed homicide or suicide, which were frequently observed in other parts of Africa. This book is not the last word about psychiatry in Ghana, but it is an important contribution to the study of mental disorders in Africa. It is full of interesting anthropological and clinical observations. Dr. J. R. Rees does not overstate its value when he says in his foreword that it should be obligatory reading for all who were concerned with the medical and social problems of Africa.

E. STENGEL.

CELL NUCLEUS

The Cell Nucleus. Proceedings of an Informal Meeting held by the Faraday Society, August 31–September 1, 1959. Chairman: Professor J. S. Mitchell, F.R.S. (Pp. 269+xiii; illustrated 50s.) London, Toronto, Sydney, Wellington, Durban: Butterworths. 1960.

This book contains the papers presented at an informal meeting held at the Department of Therapeutics, University of Cambridge, in 1959 and organized by the Faraday Society. When my attention is drawn to this type of book my response is: "What, another?", so I was agreeably surprised to find that this is not just one more of those collections of rather lengthy, and usually tedious, recapitulations of his own work that the modern peripatetic electron-microscopist, travelling from one symposium to another, feels bound to issue for the edification of the scientific world. The reason for this, I think, is the relatively large number of individual

contributions — thirty-eight—and their brevity, the shortest occupying half a page and the longest 28 pages.

Thus we are presented with accounts of work in which a very wide variety of techniques have been employed in elucidating the structure and function of the nucleus. For example, the study of the nucleolus has involved, of course, the electron-microscope, but, in addition, the ultra-violet microwave, which permits the investigator to destroy a single nucleolus in the living cell and study the effect of this on the incorporation of P-32-labelled phosphate or tritiated cytidine into the R.N.A. Or in place of the ultra-violet light he may use a narrow pencil of *x* rays, and study the effects of nucleolar destruction on synthesis of R.N.A. as measured by ultra-violet absorption. Or in place of either of these methods he may use more classical genetic techniques of breeding from mutants of frogs containing one or no nucleoli in their nuclei and demonstrating the dependence of viability on the presence of at least one nucleolus. The study of the remaining features of the nucleus has likewise entailed the application of many techniques, ranging from the electron-microscopy of chromosomes, through biochemical studies of centrifuged fractions of cell structure, the use of autoradiography in assessing synthetic activity, and the study of the enzymology of isolated nuclei, to the application of various physico-chemical studies of the bonding between nucleic acids and proteins. In reading the individual papers I felt that the authors were imparting something new and not just recapitulating earlier work.

As a general rule I feel that the lucubrations at symposia and congresses should not be published, as this presents the modern librarian with an intolerable burden, both of weight and expense, in loading his shelves with what usually turns out to be redundant literature. There are some exceptions, however, and this is one.

HUGH DAVSON.

BOOKS RECEIVED

Review is not precluded by notice here of books recently received.

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INDICATIONS FOR ERYTHROMYCIN

There appears to be some disagreement about the present place of erythromycin in therapeutics. At the time of its discovery and for some time afterwards it was rightly regarded as the last line of defence against serious staphylococcal infections resistant to earlier antibiotics. Because there was a danger that these organisms might become resistant to erythromycin, too, its use was severely restricted in Great Britain as the result of repeated authoritative advice and in New Zealand even by governmental direction. The continuation of this policy has created in some minds an idea that to prescribe erythromycin is a serious step, only to be taken in exceptional circumstances. It has even been translated into a belief that the drug is dangerous, whereas, in fact, serious toxic effects from it are very rare.

It is at least arguable that the situation calling for these restrictions no longer exists. Erythromycin is not now the last and only resort in the treatment of resistant staphylococcal infections. It has been followed not only by other antibiotics of the macrolide group, but by novobiocin, which is highly active against staphylococci, by vancomycin and ristocetin, also active and likely to remain so because resistance to them is acquired with great difficulty, and finally by the newer penicillins, notably methicillin. Admittedly the administration of any of the last three is scarcely feasible in domiciliary practice, but it is no longer possible for a patient in hospital to be left to his fate because there is no antibiotic to which his staphylococcus is sensitive. This is the situation which was feared in the early 'fifties.

If it is now permissible to use erythromycin more freely, what are the indications for it? Erythromycin has a closely similar range of activity to that of penicillin, embracing notably all the pyogenic cocci. It is thus an alternative to penicillin for the treatment of acute streptococcal sore throat and other manifestations of streptococcal sepsis, and of lobar pneumonia and other pneumococcal infections. It may be added that both sulphonamides and tetracyclines are also usually suitable for these purposes, and the choice between them all is best made on the basis of individual experience. As compared with penicillin, erythromycin has the advantage that hypersensitivity is never a bar to its use; on the other hand it attains only moderate concentrations in the blood, even when given in the better-absorbed form of the propionyl ester, whereas penicillin can, if necessary, be made to attain higher ones by greatly increasing the dose. Staphylococcal infections may also be an indication for it, and staphylococci are—at least at present in Great Britain—much more often resistant to penicillin than to erythromycin.

If erythromycin were used more freely, what is the danger that its value may diminish owing to acquired bacterial resistance? In the first place this danger exists only so far as is known in connexion with the staphylococcus. Indiscriminate use is naturally to be deplored. Neither this nor any other antibiotic should be given without some reasonably clear idea of what it is intended to achieve: as a general rule the patient should be undoubtedly ill and at least in some possible danger of becoming worse. If such criteria were accepted, they would limit consumption to a reasonable and probably safe level, certainly a lower one than has existed in some countries.

It is sometimes suggested that there should be an agreed policy for the use of antibiotics designed to preserve their therapeutic activity. Some hospitals have such a policy, and in a few areas it has been suggested that general practitioners should also follow it. Apart from restriction to necessary indications, which is much the most important feature of any such programme, it may encourage the prescribing of as wide a variety of suitable antibiotics as possible, or alternatively confine prescribing to a few, abandoning any to which resistance is developing and substituting a different antibiotic. Another but expensive policy designed to prevent bacterial resistance and now under trial at Hammersmith Hospital is the regular prescription of combinations of two drugs.[1] Measures of this kind may be necessary in hospitals, where antibiotics are of necessity extensively used, and where any resistant strains of bacteria which appear are then favoured by their environment and thus apt to cause extensive cross-infection. The circumstances of domiciliary practice are different; no such evil consequences are at all likely to follow the emergence of a resistant strain. All the evidence points to hospitals as the source of these problem bacteria, and little or none to their origination in the home. It therefore seems that the individual general practitioner may reasonably be entitled to a little more latitude than his

[1] Barber, Mary, *et al.*, *Brit. med. J.*, 1960, **1**, 11.

hospital colleagues in prescribing some of these drugs whose future value may depend on how discriminately we use them.

VAGOTOMY FOR PEPTIC ULCER

Vagotomy was reintroduced for the surgical treatment of the chronic duodenal ulcer by Dragstedt in 1943. There was an initial wave of enthusiasm for this operation because it was hoped that it would be free of all the disadvantages of the more mutilating operation of partial gastrectomy. It rapidly became clear that vagotomy alone was so frequently complicated by gastric stasis that some form of drainage operation should be combined with it. Gastroenterostomy, pylorectomy, and pyloroplasty all have been tried, principally the first. By now very large numbers of these operations have been carried out by surgeons all over the world, and it seems surprising that there should still be doubt about the merits of vagotomy and drainage as compared with partial gastrectomy; yet this is very much the case.[1]

It is worth while examining the reasons for this difference of opinion in the face of what at first sight would appear to be ample evidence on which to come to a conclusion. Probably the differences in results between these two operations are, in fact, comparatively small, and thus only large series of cases are likely to reveal them. It is therefore not surprising if individual surgeons continue to get better results with the operation which they believe to be the better and therefore practise the more frequently, especially for the routine uncomplicated case. Moreover, while it is relatively easy to compare the incidence of such things as operative mortality and ulcer recurrence rate in series of different operations, it is much more difficult to make a comparison between the various symptoms responsible for the post-operative morbidity that is the greatest problem in the surgical treatment of ulcer.

Probably the largest series of cases is that collected by the American Gastroenterological Association,[2] in which 2,441 cases of vagotomy and gastroenterostomy carried out by various surgeons were compared with 1,030 of partial gastrectomy for duodenal ulcer. These results showed that over 90% of patients who had had either operation stated that they were satisfied with the result. The operative mortality of vagotomy was lower (1.4%) than that of partial gastrectomy (2.57%), but the proved recurrence rate was higher (2.4% compared with 1.6%). The length of follow-up was comparatively short, and it is possible that the stomal ulcer rate in the vagotomy group might have been considerably higher after a further passage of time, as late recurrences are not uncommon after simple gastroenterostomy, while they are comparatively rare after partial gastrectomy. In Great Britain A. V. Pollock[3] collected the results of vagotomy carried out at various centres and reported an operative mortality rate of 1.27% and a known recurrence rate of 1.7%. In contrast are the results of other surgeons such as G. Slaney, P. G. Bevan, and B. N. Brooke,[4] who have abandoned the operation because of the high incidence of recurrence. They had a known recurrence rate of 24 out of 91 cases, while G. F. Henson and C. G. Rob[5] reported 11 out of 100. As to other complications, accurate evidence is scanty, but Pollock found the incidence of severe diarrhoea to be 16% and of mild diarrhoea no less than 53% after vagotomy.

Thus, if all the available evidence is considered, it would appear that both types of operation are satisfactory in the majority of patients at present selected for surgical treatment, but a minority have trouble after either operation. While vagotomy and gastroenterostomy is the slightly safer operation, it probably carries a higher incidence of recurrent ulcer.

Several developments may alter the picture in future. Some carefully controlled comparisons of the two operations are being carried out at surgical centres in Great Britain, and technical developments may diminish the disadvantages of vagotomy. H. W. Burge[6] has shown that the number of branches of the vagi is very variable, and the higher recurrence rate in the vagotomy series is probably due in part at least to incomplete vagotomy. He has therefore developed a technique of vagal stimulation at the time of operation which shows by the presence or absence of gastric contractions whether the vagi have all been divided or not, enabling a search to be made for any finer unseen branches. This is, in theory at any rate, far more satisfactory than carrying out post-operative insulin test meals to assess this point. Secondly, in order to reduce the post-operative morbidity of the vagotomy group further work is needed on the mechanisms responsible for the development of diarrhoea in some patients but not in others. Burge has suggested that this may be due in part to section of the vagal nerve supply of the pancreas, and he now advocates a vagotomy which will section the branches supplying the stomach but leave all others intact. The results in a large series of patients treated by this method would be of very great interest.

[1] Dragstedt, L. R., *et al.*, *Proc. roy. Soc. Med.*, 1959, **52**, 835.
[2] Jordan, M. S., *Gastroenterology*, 1951, **19**, 599.
[3] Pollock, A. V., *Lancet*, 1952, **2**, 795.
[4] Slaney, G., Bevan, P. G., and Brooke, B. N., ibid., 1956, **2**, 221.
[5] Henson, G. F., and Rob, C. G., *Brit. med. J.*, 1955, **2**, 588.
[6] Burge, H. W., *Ann. roy. Coll. Surg. Engl.*, 1960, **26**, 231.

IMMUNOLOGICAL ASPECTS OF RHEUMATISM

We have long been accustomed to think of rheumatic fever and rheumatoid arthritis as being in some way connected. Pathologists have shown morphological similarities in the lesions of the two diseases, and argued by analogy with experimental results that they represented hypersensitivity reactions. Feeling about the association of the two conditions has moved first this way and then that. Perhaps the last occasion when they seemed to stand in close relation with each other was ten years ago, when the first dramatic successes of cortisone in promptly relieving the symptoms of both diseases were observed. To-day they are drifting into separate compartments of medical thought, except for the widely held and reasonably substantiated hypothesis that the pathogenic mechanism in both involves some form of immunological response, leading through abnormal tissue reactivity to sterile granulomatous lesions in the connective tissues.

An immunological response of this kind implies the presence of a provocative antigen. In the case of rheumatic fever we identify the source of this with the *Streptococcus pyogenes*, and this disease has now come largely under control through the use of hygienic measures and therapeutic agents truly effective against the streptococcus. We now know enough about rheumatic fever to satisfy the doctor in us, though the scientist in us may still reflect that we really understand nothing about the mechanism of the disease.

No part of us can be satisfied about rheumatoid arthritis. We do not know how to prevent it, our treatments offer only alleviation and no cure, and the causative agent of the disease is as obscure as its pathological mechanism. Since years of observation have failed to uncover an exogenous antigenic agent in this disease of a supposedly hypersensitive nature, it is not surprising that our hopes should become centred on the now popular concept of autoimmune disease.

Immunology is to-day a complex subject, covering such reactions as anaphylaxis and the Arthus phenomenon, both of which depend on circulating antibodies of precipitating type, and the delayed or tuberculin-type of hypersensitivity, which does not. An important and intricate branch of the subject now concerns the behaviour of homografts. Consequently it is no simple matter to judge whether or not immune responses to autogenous products may play a role in the causation of rheumatoid arthritis. L. E. Glynn and E. J. Holborow, in an admirable review recently published,[1] come to the conclusion that they can, or rather, to quote their own cautious words, "that autoimmune phenomena are probably of significance in the pathogenesis of rheumatoid disease," but they acknowledge that the case is still far from proved. Part of the argument is the old one that the vascular and subcutaneous lesions have much in common with those induced experimentally by immunological procedures, and are usually populated with plasma cells. But this only suggests that we are concerned with hypersensitivity disease in general. It is the newer work with the serological reactions, especially with the rheumatoid factor, first discovered by E. Waaler in 1940[2] and rediscovered by H. M. Rose and his colleagues eight years later,[3] that point more particularly to an autoimmunity mechanism, for certain properties of rheumatoid serum suggest that the factor is an antibody capable of reacting with potential antigens in the patient. The rheumatoid factor is a γ-globulin, but one with large molecules and a sedimentation coefficient of 19S. Though most normal γ-globulins, and with them most antibodies, have smaller molecules and a sedimentation constant of 7S, the 19S group of γ-globulins is known to contain certain antibodies as well as macroglobulins that appear only in pathological states.[4] Moreover, like antibodies in general, the rheumatoid factor has now been detected in the cytoplasm of plasma cells at various stages of maturity in the synovial tissues, lymph nodes, and occasionally the nodules of patients with rheumatoid arthritis.[5]

The question that naturally arises is whether we can identify the antigen to which the rheumatoid factor is an antibody, if, indeed, it is an antibody at all. To this there is no easy answer. The factor reacts with a number of things, including aggregated γ-globulin from various animals as well as man. Glynn and Holborow believe that the rheumatoid patient responds, by means of the rheumatoid factor, to a degree of change in autogenous proteins that the normal individual "ignores." Chemical or physical changes in γ-globulin may frequently occur in man and may supply the antigen to which the rheumatoid factor relates, but as yet we have no proof that such an autoimmune mechanism plays any part in the causation of the disease. Indeed, the pattern of tissue reaction in chronic rheumatism largely resembles the delayed or tuberculin-type of hypersensitivity reaction,

[1] Glynn, L. E., and Holborow, E. J., *Ann. rheum. Dis.*, 1960, **19**, 197.
[2] Waaler, E., *Acta path. microbiol. scand.*, 1940, **17**, 172.
[3] Rose, H. M., Ragan, C., Pearce, E., and Lipman, M. O., *Proc. Soc. exp. Biol. (N.Y.)*, 1948, **68**, 1.
[4] Kunkel, H. G., Franklin, E. C., and Muller-Eberhard, H. J., *J. clin. Invest.*, 1959, **38**, 424.
[5] Mellors, R. C., Heimer, R., Corcos, J., and Korngold, L., *J. exp. Med.*, 1959, **110**, 875.
[6] Good, R. A., Rötsiein, J., and Mazzitello, W. F., *J. Lab. clin. Med.*, 1957, **49**, 343.
[7] *Brit. med. J.*, 1960, **2**, 1446.

and is therefore probably independent of the presence of circulating antibodies. This view is supported by the observation that rheumatoid arthritis has often developed in patients with agammaglobulinaemia.[6]

Few, if any, of the speakers at a recent Empire Rheumatism Council symposium on immunology in the rheumatic diseases[7] reached the point of explaining how any of the various immunological phenomena they discussed could have a role in the origin and maintenance of rheumatoid arthritis. These phenomena, because they are hardly ever to be observed in healthy persons, have inspired a voluminous output of research papers, but we are still far from being assured that immunology will necessarily be the key that turns the last lock to reveal the secrets of this disease. It is worth remembering, perhaps, that rheumatic fever has to a large extent been conquered as a result of researches that have none the less failed to elucidate its detailed mechanism.

SERUM ENZYMES IN MYOCARDIAL INFARCTION

While cardiographic evidence of myocardial infarction is closely correlated with raised values of the serum glutamic oxaloacetic transaminase (S.G.O.T.),[1] abnormal serum values are encountered in other diseases, particularly in the presence of shock. Consequently, the search has continued for specific abnormality of serum enzymes which may reflect disease of individual organs. Interest has focused on glycolytic enzymes, allied to the transaminases, which metabolize glycogen to pyruvic or lactic acids and which abound in skeletal muscle, heart muscle, and the liver.

Transient increase of serum aldolase, an enzyme concerned with fructose metabolism, is found in acute myocardial infarction.[2] Two types of aldolase have been defined: the activity of muscle aldolase is limited to fructose 1:6-diphosphate, while liver aldolase is also active on fructose-1-phosphate.[3] J. C. Dreyfus and his associates[4] hope to trace the origin of serum aldolase by studying the action upon fructose-1-phosphate. Serum activity is determined by incubation with the substrate and colorimetric estimation of the triose phosphates so produced.[5] The range of normal values is 2 to 10 units per ml. serum.

The ability of lactic dehydrogenase (LD) to oxidize lactic acid to pyruvic acid has been recognized for many years, but this enzyme, in the tissues, preferentially converts pyruvic to lactic acid and thereby plays an important part in anaerobic glycolysis. This reversible reaction requires the presence of diphosphonucleotide, or coenzyme I. The methods for estimation of LD activity in the serum depend on the changes of ultraviolet absorption of this coenzyme on oxidation[6] or reduction.[7] Normal serum values range from 100 to 600 units per ml. A striking increase is found 24 hours after myocardial infarction, and increased activity may persist for at least a week after the acute episode.[2] This gives an advantage over S.G.O.T. determinations, but both methods share the same lack of specificity.

The knowledge that LD was a zinc-protein complex led E. S. Vesell and A. G. Bearn[8] to investigate the electrophoretic properties of this enzyme. In normal serum LD activity was located (in order of magnitude) in the α_2, α_1, and β globulin fractions. After myocardial infarction maximal activity was present in the α_1 globulin fraction, while in acute leukaemia the percentage of LD activity in the α_2 peak was increased. These changes were recorded despite normal total serum LD activity in some patients.

With further fractionation F. Wróblewski and his associates[9] have recently outlined a more detailed electrophoretic pattern for this enzyme. They described five distinct forms, or isoenzymes, of LD in human plasma (pLD_1 to pLD_5). The normal plasma had a typical composition $pLD_2 < pLD_1 < pLD_3 < pLD_5 < pLD_4$, and human tissues containing LD each had a characteristic isoenzyme composition. Cardiac muscle contains LD_4 and LD_5, with a preponderance of the latter, which is reflected in the plasma after myocardial infarction. The report suggested that quantitative estimation of plasma isoenzymes provided a more sensitive, specific, and lasting indicator of myocardial infarction than total LD or S.G.O.T. measurements. Chemical separation of these isoenzymes has not yet been reported, and the influence of similar enzymes, such as malic dehydrogenase, or the quantitative effect of zinc on the electrophoretic pattern still awaits definition.

ELECTRONARCOSIS

The administration of an electric current to induce anaesthesia has been tried from time to time, but it has not so far gone beyond the experimental stage. In the development of this idea—as of many others—Nature has anticipated Man, for some species of fish, notably the electric eels, use a strong electric discharge to paralyse and narcotize their prey. The French physicist S. A. N. Leduc pioneered electronarcosis for surgical purposes at the beginning of this century, and was able to perform major operations on dogs rendered anaesthetic, or at least non-reactive, by administering electric pulses of square-wave form. This work and the sporadic investigations that followed have been reviewed by A. Flach.[1]

Since all nervous activity is accompanied by electrical changes, it might seem at first that electric currents would be more appropriate than drugs for influencing it. However, bone is a poor conductor, and the skull forms a fairly effective barrier to the production of precisely controlled electric fields within the brain from

[1] La Due, J. S., Wróblewski, F., and Karmen, A., *Science*, 1954, **120**, 497.
[2] White, L. P., *New Engl. J. Med.*, 1956, **255**, 984.
[3] Herz, H. G., cited by Dreyfus *et al.*, in *Ann. N.Y. Acad. Sci.*, 1958, **75**, 235.
[4] Dreyfus, J. C., Schapira, G., and Schapira, F., *Ann. N.Y. Acad. Sci.*, 1958, **75**, 235.
[5] Sibley, J. A., and Lehninger, A. L., *J. biol. Chem.*, 1949, **177**, 859.
[6] Hill, R. R., and Levi, C., *Cancer Res.*, 1954, **14**, 513.
[7] Vallee, B. L., and Wacker, W. E. C. *J. Amer. chem. Soc.*, 1956, **78**, 1771.
[8] Vesell, E. S. and Bearn, A. G., *Proc. Soc. exp. Biol. Med.*, 1957, **94**, 96.
[9] Wróblewski, F., Ross, C., and Gregory, K., *New Engl. J. Med.*, 1960, **263**, 531.

[1] Flach, A., *Anaesthesist*, 1958, **7**, 180.

electrodes on the scalp. Leakage paths through the foramina and across the venous sinuses and other blood vessels impose a pattern of distribution on the current which may be far from that desired. In spite of this difficulty, there have been reports from several Continental countries, and recently in the newspapers from the U.S.A., of the production of electronarcosis in animals and man, but they do not give the impression that the method has much to recommend it. A stage of excitement often precedes narcosis; it is sometimes accompanied by respiratory difficulties and by a feeling of impending dissolution. Muscular relaxation is variable, and the margin between electronarcosis and electroconvulsion may be narrow. A grave disadvantage is the possibility of causing permanent damage to the brain. That gross damage has not been reported in animals means nothing, and properly controlled observations on man with a view to excluding the occurrence of minor damage—akin to the personality changes which may follow prefrontal leucotomy—do not appear to have been made. Complete reassurance on this point is needed before any future can be seen for electronarcosis.

HYPOTHERMIA AND THE EFFECTS OF COLD

Our present understanding of hypothermia is a far cry from Larrey's observations on localized chilling in 1812, and even Temple Fay's work of a mere 20 years ago. But the foundations of what is now complacently called moderate hypothermia were laid by Hegnauer and Bigelow in the early 1950's, soon to be followed by the introduction of profound hypothermia. In this short space of time the clinical achievements have been spectacular, while our eyes have been opened to the new and virtually unknown fields of pharmacology and physiology at temperatures other than normal. That these have been previously disregarded is understandable when one realizes that poikilothermic man develops a remarkable resistance or protective mechanism towards the effect of cold. Even the Eskimo and the Australian aborigine, who are subjected to great changes of temperature, show little acclimatization of the body as a whole. Adaptive changes do occur, but there is a wealth of difference between living in a cold environment and being suddenly subjected to hypothermia for surgery. Hitherto, therefore, a reduction of total body temperature has seemed as incompatible with life as hyperpyrexia. Indeed, many of the problems encountered during the development of hypothermia, ventricular fibrillation in particular, lent support to this belief. Thus 28° C. (82° F.) appeared to be the lowest safe limit to which a patient might reasonably be subjected. To C. E. Drew, G. Keen, and D. B. Benazon[1] goes the credit for taking the logical step of substituting an extracorporeal circulation for a non-functioning heart, and continuing the cooling process. Though this may have seemed a sound theoretical progression of thought, it has been made practicable only by immense technical advances and painstaking experiment.

This latest specialty is unlikely to remain the exclusive domain of a few surgeons and anaesthetists much longer, for possible uses of hypothermia are foreseen as an adjunct to deep *x*-irradiation and for reducing cerebral activity as an alternative to electroplexy in psychiatry. It is hard to imagine any other field of medicine which has progressed so rapidly, carrying with it the equally remarkable developments in cardiac surgery. Books on hypothermia are thus almost out of date by the time they reach the bookstalls. For this reason alone, the extensive review of the whole field to which the latest issue of the *British Medical Bulletin*[2] is devoted under the editorship of Dr. A. S. Parkes, F.R.S., serves a most valuable purpose. As a source of up-to-date information on progress in medicine it has a practical use; to the non-expert the 15 articles written by acknowledged authorities offer a fascinating report on man's inventiveness.

DIET AND ATHEROSCLEROSIS

If recent research into the causation of atherosclerosis has shown anything with certainty, it is that this disease, or group of diseases, develops from a complex of causes, not one alone. Heredity, lack of exercise, and too much animal fat in the diet all have their advocates as major causes; the fashionable concept of auto-immunity is finding favour in this field, while the idea that mental stress has a prime role is perhaps tending to drop back a bit. Diabetes, hypertension, and cigarette smoking are also considered to play a part in its aetiology. A piece of advice recently issued by the American Heart Association[1] is therefore of topical interest, especially as it takes cognizance of a variety of possible causes but firmly cuts out disputation. It states: "The reduction or control of fat consumption under medical supervision, with reasonable substitution of poly-unsaturated for saturated fats, is recommended as a possible means of preventing atherosclerosis and decreasing the risk of heart attacks and strokes. This recommendation is based on the best scientific information available at the present time." The report also recommends "regular, moderate exercise, exemplified by walking," as desirable, and refers to the increased risk attending a strong family history of atherosclerosis.

The patients who should modify their diet in accordance with the report's suggestions are divided into three categories. The first is people who are overweight; they are advised to reduce the fat content of their diet and take more exercise. Secondly, a diet moderate in calories and fat, and in particular substitution of unsaturated for a substantial part of the saturated fat, is recommended for men who have a strong family history of atherosclerosis, raised levels of blood-pressure and blood cholesterol, are overweight, "and/or who lead sedentary lives of relentless frustration." Thirdly, patients who have had one or more atherosclerotic heart

[1] Drew, C. E., Keen, G., and Benazon, D. B., *Lancet*, 1959, **1**, 745.
[2] *British Medical Bulletin*, 1961, **17**, 1-78. (British Council, 65 Davies Street, London W.1. 20s. net.)

[1] Report by the Central Committee for Medical and Community Program of the American Heart Association, *Circulation*, 1961, **23**, 133.
[2] Pilkington, T. R. E., Stafford J. L., Hankin, V. S., Simmonds, F. M., and Koerselman H. B., *Brit. med. J.*, 1960, **1**, 23.
[3] Lloyd, J. K., and Jukes, H. R., *Lancet*, 1961, **1**, 312.

attacks or strokes are advised to change their diet. Details of an unsaturated-fat diet, and a trial of it in a small group of patients in their homes, were reported by T. R. E. Pilkington and colleagues last year.[2] (A diet with the same function has also recently been described for the treatment of children with diabetic and other forms of hypercholesterolaemia.[3]) Finally, the following quotation from the American Heart Association's report expresses the common-sense view: "Fat is an economical and, in limited amounts, a wholesome food. Food faddism of any sort should be avoided and significant changes in diet should not be undertaken without medical advice."

ABDOMINAL WOUND DEHISCENCE

Separation of the tissues of the abdominal wall after operation can mar an otherwise satisfactory result. Complete dehiscence is not only unpleasant for the patient but carries an associated mortality due to infection, obstruction, or pulmonary embolism. Partial or complete separation of the layers deep to the skin causes an unsightly hernia and may result in intestinal obstruction due to adhesions or incarceration. However, wound dehiscence is not common, and the surgeon tends to accept the occasional case as the inevitable price to be paid for the benefits of laparotomy.

The causes of the condition have been much disputed. It is commonest after the vertical incisions which are necessary to give adequate exposure in extensive abdominal procedures, and is particularly prone to follow the lower abdominal incisions such as are employed in gynaecological surgery. When the patient attempts to cough, the oblique abdominal muscles pull directly on the suture line and place great stress on the site of the repair of these wounds. Dehiscence is more likely to occur in those patients who are fat, malnourished, or have neoplastic disease in the abdomen.

The rarity with which this complication occurs in children and adolescents suggests that technique is not the major factor in aetiology. When a burst abdomen is explored it is seldom found that the suture material, whatever its nature, has given way. In most cases the stitches have cut through softened, friable fascia; this is particularly noticeable in infected wounds. Although infection is the most potent cause of such tissue softening, some of the suture materials themselves engender a similar reaction: of these catgut is the worst offender. The action of catgut was discussed in these columns recently.[1] It commonly excites an inflammatory response, which leads to tissue softening in the neighbourhood of the sutures; its great advantage is that it is absorbed if organisms invade the wound and does not give rise to persistent sinuses, though this advantage is apt to be offset by the effects of the inflammatory response. Silk and thread also excite a similar reaction, though to less degree, but they suffer from the grave disadvantage that infection is prolonged by them if it occurs. Monofilament nylon does not cause much tissue reaction, nor does it harbour infecting organisms, but it is not particularly easy to handle. It may snap, or eventually be discharged after operation.

Stainless steel wire has been advocated on many occasions,[2 3] and recently a further paper has appeared extolling its virtues.[1] It is little stronger than the other materials and has the disadvantage of being awkward to use. However, A. Lawrence Abel and A. Clain[4] claim to have eliminated wound dehiscence by using it, and many surgeons have found that it does indeed reduce the frequency of the burst abdomen. Wire cuts through softened tissue as it cuts through cheese, so it might be thought that wounds would break down more often when sutured with it. That they do not do so is probably because the wire causes only minimal tissue softening, an assumption which is supported by the observation that wire does not prevent dehiscence in infected wounds, where the tissues are softened by bacterial inflammation. If a wound does become infected, wire sutures will not prolong infection nor be extruded. A few months after insertion, steel wire breaks up into fragments due to metal fatigue, but by this time tissue union is complete. Abel and Clain particularly stress the usefulness of stainless steel wire for suturing large incisional herniae and give an account of their own technique which is both stimulating and helpful. Though not everyone will agree that wire suturing is the complete answer to the difficulties these cases present, it certainly deserves wider trial. Its advantages more than outweigh technical difficulties in handling. These ideas are based on clinical impressions. What would be helpful is a controlled trial of various materials in comparable wounds to test whether wire or some other material gives the best suture in the abdominal wall.

[1] See *Brit. med. J.*, 1960, **1**, 1005.
[2] Abel, A. L., and Hunt, A. H., ibid., 1948, **2**, 379.
[3] Cattell, R. B., *Surg. Clin. N. Amer.*, 1942, **22**, 795.
[4] Abel, A. L., and Clain, A., *Brit. J. Surg.*, 1960, **48**, 42.

SHEFFIELD MEETING

Though the Annual Meeting of the B.M.A. has just been held in New Zealand, a meeting slightly shorter than is usual in the summer will be held at Sheffield in July. The medical profession there, the university, and the civic authorities will be extending their hospitality to the Annual Representative Meeting and then to a 2½-day clinical meeting. A provisional programme is published in the *Supplement* this week. It includes a list of hotels so that members may have the opportunity of booking rooms in good time. Accommodation in university halls of residence is also available, while the hardier spirits who go by caravan will find that they too are well catered for. Some of the important, and it may be hoped controversial, themes to be discussed in the clinical sessions are: prolonged pregnancy; the naughty child; the changing pattern of acute infections; management of anaemia; radiation disorders; swollen legs; incontinence in adults; liver disease; diuretic therapy; and diseases of eye and skin. An entertaining round of visits and dinners has also been arranged. Whatever his particular interests, the practising doctor is sure to find something novel and stimulating at the meeting, not least in the informal exchange of views with other members there.

Clinicopathological Conference

A CASE OF MALIGNANT HYPERTENSION

DEMONSTRATED AT THE

POSTGRADUATE MEDICAL SCHOOL OF LONDON

This is the case of a man with malignant hypertension treated at Hammersmith Hospital for nine years with hypotensive drugs. For five years he remained well and did full-time work. He developed pulmonary and neurological complications (Case No. 123,189; P.M. No. 9,066).

Clinical History

Professor J. McMICHAEL: This patient, a glazier by occupation, was aged 47 at the time of his death. In 1940, at the age of 27 and while serving in the Army, he had an illness diagnosed as "nephritis." At this time he complained of abdominal pain and swelling, but there was no history of oedema or haematuria. He was discharged from the Forces as a result of this illness.

In 1951 he was first admitted to Hammersmith Hospital complaining of blurred vision and headache on waking in the morning for two months. He was passing urine once during the night, but had no other symptoms. No family history was elicited of high blood-pressure or kidney disease. On examination he was a healthy-looking, well-built man. There were no signs of congestive heart failure. The heart was enlarged to the left and the rhythm regular. The blood-pressure was 230/140 mm. Hg. The ocular fundi showed bilateral gross papilloedema, white macular exudates, and scattered haemorrhages. The urine contained a moderate amount of protein; there were no pus cells or casts in the centrifuged deposit. The blood urea was 70 mg./100 ml.; cholesterol 307 mg./100 ml.; serum proteins 7.2 g./100 ml. (albumin 4.6 g., globulin 2.6 g.). A chest radiograph showed left ventricular enlargement, with clear lung fields. Intravenous pyelography was not performed in view of the raised blood urea level. He was treated with subcutaneous hexamethonium bromide, and left hospital in April, 1951, taking 70 mg. twice daily. His vision improved, and two months after his discharge the papilloedema had cleared. Increasing doses of hexamethonium were necessary, and in December, 1951, he was receiving 180 mg. twice daily, which reduced his blood-pressure to 150/110 mm. Hg, in the erect position.

DYSPNOEA AND COUGH

In April, 1952, he began to complain of shortness of breath on exertion and a dry cough. The dose of hexamethonium was raised to 240 mg. twice daily without any improvement in these symptoms. A chest radiograph at this time showed bilateral apical shadowing (Fig. 1). The blood sedimentation rate was 13 mm./hr. Six specimens of sputum were negative for tubercle bacilli. The blood urea was 82 mg./100 ml. In the ocular fundi the disks were sharp and there were now no haemorrhages or exudates. The lung lesions were considered to be probably tuberculous but inactive, and treatment was continued with hexamethonium, the dose being increased to 300 mg. twice daily.

In June, 1952, he was readmitted complaining of breathlessness, which now seriously limited his effort tolerance, and a harsh irritating cough. At this time a dose of 210 mg. hexamethonium subcutaneously was sufficient to reduce the blood-pressure to 105/80 mm. Hg with the patient standing, and this was accompanied by marked dyspnoea which was relieved by sitting down. There were no physical signs of congestive heart failure, and on auscultation of the lungs only a few scattered rhonchi. A chest radiograph now showed increased infiltration of both lungs (Fig. 2). The blood sedimentation rate was 19 mm./hr. Repeated examination of sputum and gastric washings was negative for tubercle bacilli. The blood urea was 110 mg./100 ml. The vital capacity was 1.8 litres. Treatment with streptomycin and para-aminosalicylate (and later isoniazid) was given for three months without any change in the pulmonary radiological appearances. In October, 1952, it was observed that some other patients receiving hexamethonium developed similar radiological changes; anti-tuberculous drugs and hexamethonium were therefore stopped. His vital capacity rose to 3.1 litres, and he was discharged at the end of October, symptomatically much improved, on no treatment. After discharge from hospital his blood-pressure rose again and hexamethonium was started again three weeks later, in smaller doses.

From 1953 to 1958 he continued as an out-patient, and during this time remained well and at full-time work. He was not troubled by dyspnoea. The blood-pressure was well controlled by one injection of hexamethonium at night and a small oral dose of pentolinium at mid-day (average readings 130/85–160/100 mm. Hg in the erect position). Serial chest radiographs showed slow clearing of the pulmonary shadowing, although this was incomplete, leaving a residual central pulmonary fibrosis (Figs. 3 and 4). A plain abdominal radiograph at this time showed the right renal outline, which appeared larger than normal, but did not show the left kidney clearly. The blood urea climbed very gradually, mean values during this period being: 1953—103 mg./100 ml.; 1954—98 mg./100 ml.; 1955—107 mg./100 ml.; 1956—153 mg./100 ml.; 1957—158 mg./100 ml.; 1958—190 mg./100 ml. The blood haemoglobin level was well maintained, being 13.8 g./100 ml. in 1957 and 12.8 g./100 ml. in 1958.

NEUROLOGICAL DISORDER

Dr. C. PALLIS: In September, 1958, he rapidly developed over a period of six weeks a feeling of stiffness in the thighs, cramps in the fingers, and dragging of the feet. He had no pain or paraesthesiae, and there was no difficulty in speech, swallowing, or sphincter control. He was readmitted, and on examination was noted to be thin, with partial alopecia and generalized skin pigmentation. There was a semi-pedunculated swelling on the medial aspect of the left knee. The blood-pressure was 150/110 mm. Hg. The ocular fundi showed Grade II retinopathy. The pupils were normal and there was no nystagmus or ophthalmoplegia. The jaw-jerk was brisk. There was no facial weakness, nor were there bulbar signs. Slight symmetrical wasting was present of the small muscles of both hands with corresponding weakness, and slight

wasting of both forearms. There was excellent power in the shoulder-girdle, trunk, and pelvic-girdle musculature. Both thighs showed moderate wasting with occasional fasciculation. There was wasting of the calf muscles, and gross wasting of the anterior tibial groups and peronei, which were very weak. The reflexes were normal in the upper limbs; the abdominal reflexes were retained; the lower limb reflexes were very brisk; no plantar responses could be elicited, owing to the severe muscle weakness. All sensory modalities were normally perceived. These findings led to a clinical diagnosis of motor-neurone disease.

INVESTIGATIONS

Investigations in October, 1958, included: *Blood.*—Haemoglobin 12.5 g./100 ml.; leucocytes 14,000–20,000/c.mm.; sedimentation rate 25 mm./hr.; urea 240–297 mg./100 ml.; bicarbonate 15 milliequivalents/litre; calcium 12 mg./100 ml.; phosphate 8.8 mg./100 ml.; alkaline phosphatase 13 King–Armstrong units/100 ml.; Wassermann and Kahn reactions negative. *Radiological:* Chest—no change in diffuse pulmonary fibrosis; cervical and dorsal spine—dense appearance of the bones with a close trabecular pattern. *Cerebrospinal fluid:* cells 5/cu.mm.; protein 350 mg./100 ml.; Pandy test positive; Lange 1111111000; Wassermann reaction negative. No evidence of manometric block. *Electroencephalogram:* moderately severe generalized abnormality, rhythmic activity being predominantly within the theta range. *Electromyogram:* (left tibialis anterior) findings suggestive of chronic denervation (fibrillation potentials and grossly reduced interference pattern). *Biopsy of mass from left knee:* neurilemmoma.

No treatment other than antihypertensive therapy was given (pempidine was substituted for hexamethonium in January, 1959). The neurological condition did not progress after the onset. He was admitted to hospital again for reassessment in July, 1959, when the physical findings and laboratory investigations were substantially the same as ten months previously. The C.S.F. protein was still grossly increased, at 230 mg./100 ml. Neither clinically nor electro-myographically was there any evidence of nerve regeneration. Death occurred in January, 1960, after a short illness characterized by increasing drowsiness.

Clinical Diagnosis

(1) Malignant hypertension.
(2) Chronic renal disease (?) nephritis.
(3) "Hexamethonium lung."
(4) ?Motor-neurone disease.

Post-mortem Findings

Dr. B. E. HEARD: The body was that of a man weighing 10 stone (63.5 kg.) and height 5 ft. 9 in. (1.73 m.).

The pleural sacs and pericardium each contained about 200 ml. of serous fluid. The *heart* weighed 595 g. (normal, 370 g.). There was a fibrinous pericarditis which had become partly organized and was not easily stripped from the heart. The left ventricle was hypertrophied to 20 mm. and the right ventricle to 5 mm. in the outflow tracts. The mitral and aortic valves were normal in circumference but the pulmonary valve was dilated to 95 mm. (normal, 85 mm.), and the tricuspid valve was dilated to 145 mm. (normal, 130 mm.). There was an aneurysm of the membranous part of the interventricular septum 1 cm. in diameter. On the right it projected into the ring of the tricuspid valve and replaced about 1 cm. of its circumference. There was no perforation. The coronary arteries were widely patent but showed moderate atheroma. The aorta showed increasing atheroma beyond the arch with fibro-fatty plaques 2 cm. or more across. The veins were normal.

The *oesophagus, stomach,* and *small and large intestines* were normal. The *liver* was enlarged to 2,350 g. (normal, 1,600 g.) and showed mild centrilobular congestion. The gall-bladder and bile ducts were normal. The *pancreas* was normal.

PULMONARY LESIONS

The trachea and the main bronchi contained some mucopus. The right *lung* weighed 860 g. (normal, 450 g.) and the left weighed 760 g. (normal, 400 g.). Externally they showed irregular grooving, especially over the upper lobes, and they appeared somewhat shrunken. The left lung was prepared by pressure fixation. The lower three-quarters of the upper lobe and middle part of the lower lobe showed fibrosis and irregular shrinking and the fine air-space walls were distorted. Bronchi were dilated and fibrosis was heavier in these areas. Histologically fibrous parts of the lung showed some degree of thickening of the alveolar walls by fibrous tissue in which were scattered swollen elastic fibres (not impregnated with calcium) and conchoidal bodies, together with numerous foreign-body giant cells (Fig. 5). Similar fibrous tissue was lining some bronchioles, and occasionally one was completely obliterated by it. These appearances are compatible with a very late stage of hexamethonium lung. Sections of bronchi showed slight increase in the size of some mucous glands but otherwise no special features. The pulmonary arteries and bronchial arteries showed intimal thickening.

The right *kidney* weighed 310 g. (normal, 170 g.). The surface was interrupted by occasional cysts up to 2 cm. across, but generally was remarkably smooth. The capsules stripped with some difficulty. The cut surface showed advanced polycystic disease in all areas and very little surviving parenchyma. The left kidney was shrunken to 90 g. and contained a smaller number of small cysts. Histologically (Fig. 6) both kidneys showed considerable fibrosis of the surviving parenchyma and calcification of basement membranes of proximal convoluted tubules (Fig. 7). Some of the cysts were lined by numerous macrophages together with giant cells and doubly refractible crystals (Fig. 8). All arteries showed considerable fibro-elastic intimal thickening. The rest of the genito-urinary tract was normal.

The *spleen* was congested and weighed 295 g. (normal, 170 g.). The vertebral *bone* was extremely hard, as was the sternum. Histologically the trabeculae showed, in undecalcified sections (Fig. 11), osteoid seams up to 35μ thick, indicating osteomalacia. There were also small foci of fibrosis and osteoplastic activity indicating osteitis fibrosa. The *thyroid* was normal (27 g.) as were the *suprarenals* (right 8 g., left 10 g.). Two of the *parathyroids* (Fig. 9) were enlarged to a maximum diameter of 1.5 cm. and histologically showed a predominance of chief cells, with areas of oxyphil change and one area of hyperchromatism. The *pituitary* appeared normal. *Voluntary muscle* (Fig. 10) showed groups of shrunken fibres indicating secondary atrophy.

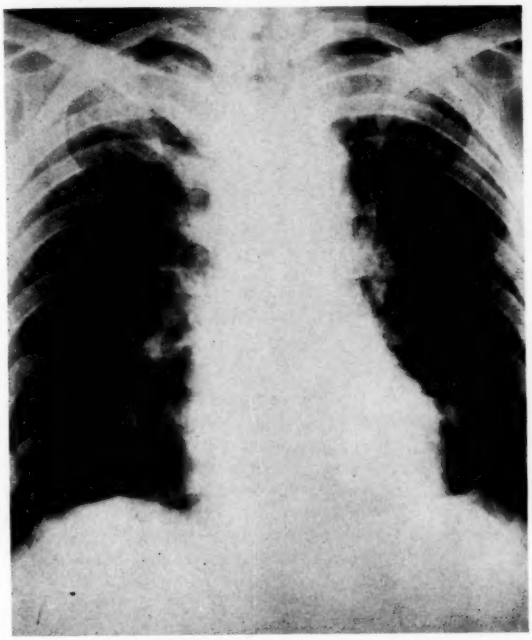


FIG. 1.—Chest radiograph (April, 1952), showing bilateral apical shadowing.

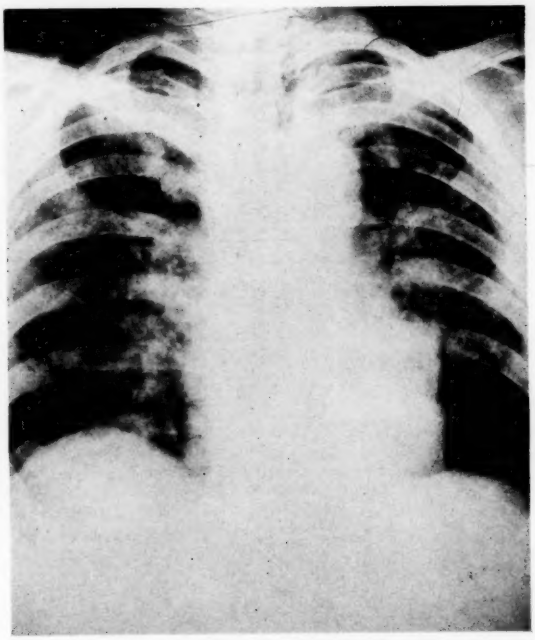
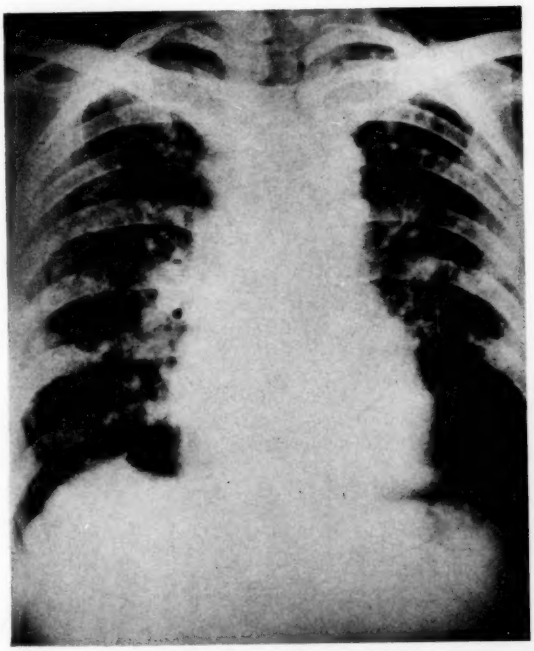
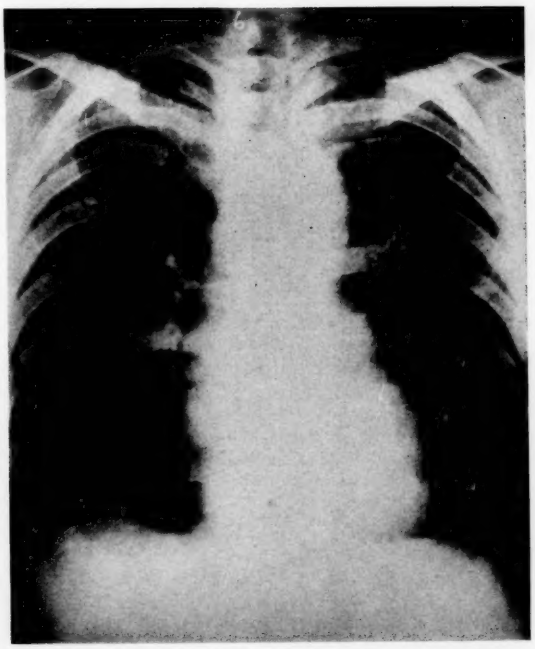


FIG. 2.—Chest radiograph (June, 1952), showing increased infiltration of both lungs.





FIGS. 3 and 4.—Serial chest radiographs (1957 and 1958) showing gradual clearing of the pulmonary shadowing, with residual central fibrosis.

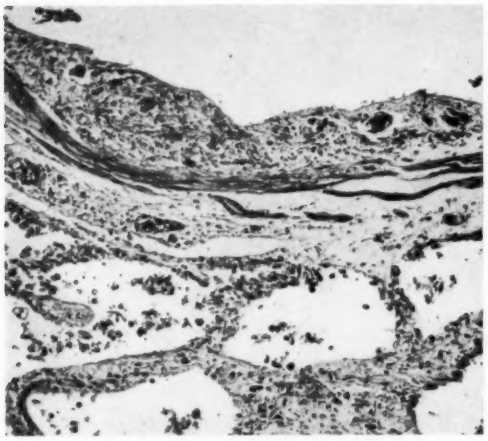


FIG. 5.—Lung shows fibrous thickening of alveolar walls and a bronchus lined by fibrous tissue containing foreign-body giant cells. (H. and E. ×100.)

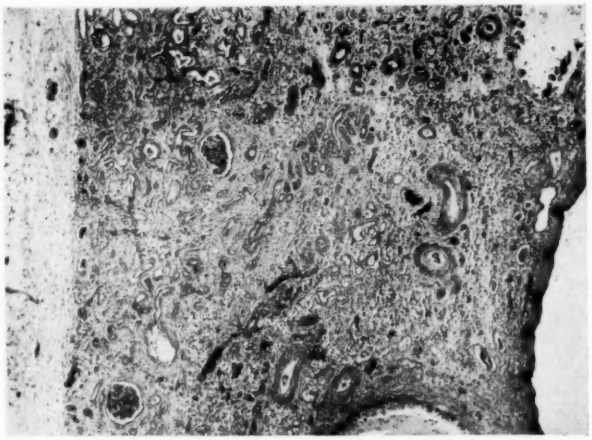


FIG. 6.—Kidney showing fibrous replacement of tubules and intimal thickening of intralobular arteries. The edges of three cysts are seen on the right. (H. and E. ×32.)

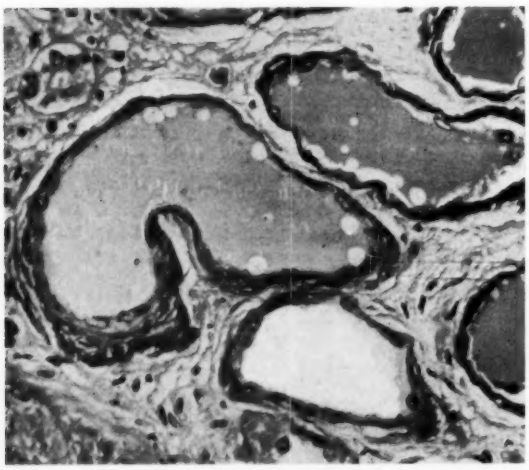


FIG. 7.—Kidney showing a group of dilated proximal convoluted tubules. There is calcification of the basement membranes seen best in the lower left quadrant. (H. and E. ×380.)

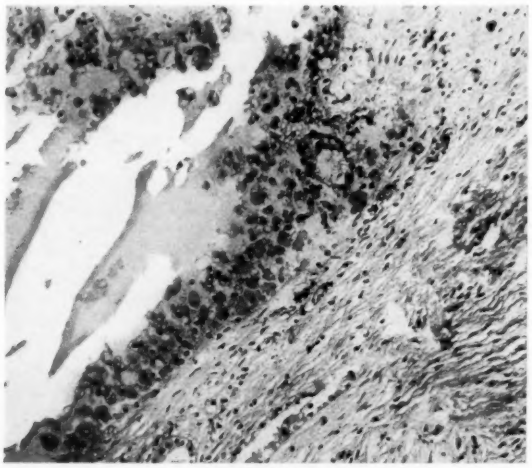


FIG. 8.—The wall of a renal cyst lined by numerous macrophages mixed with some crystalline deposits (upper right quadrant). (H. and E. ×132.)

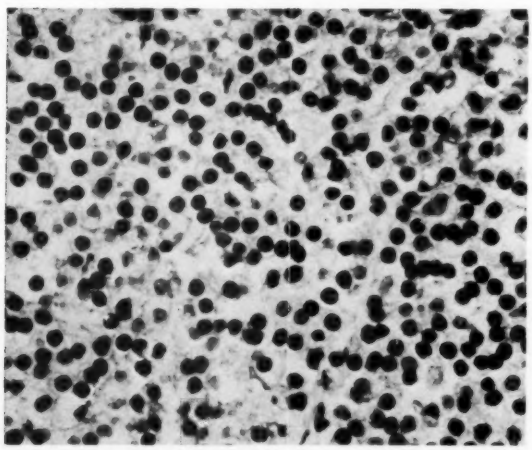


FIG. 9.—Parathyroid hyperplasia. In this area there is an even distribution of chief cells. (H. and E. ×515.)

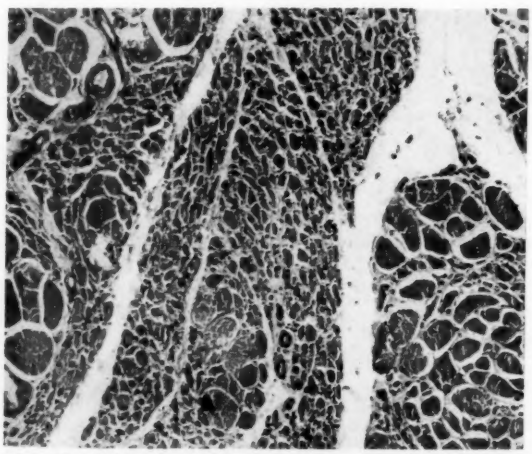


FIG. 10.—Voluntary muscle showing large areas of shrunken muscle fibres in the centre. Compare these with the normal fibres at the edges of the photograph. (H. and E. ×95.)

C.N.S. EXAMINATION

The brain weighed 1,400 g., which, with the cord, was kindly examined by Dr. W. H. McMenemey. Grossly there was very little atheroma of the cerebral arteries. In the white matter of the cerebellum there were two areas of discoloration and softening. Histologically the cerebral arterioles showed slight to moderate atheroma, but in the hippocampus there was marked capillary sclerosis with calcification. The cerebral cortex showed a status spongiosus in many places, rather more in the outer than in the inner layers, with patchy distribution, although it is to be seen in all areas examined, being most marked in the hippocampus and the lateral geniculate bodies. It was not associated with any obvious neuronal degeneration, although there was some evidence of astrocytic proliferation. In the cerebellum the Purkinje cell layer was separated from the underlying granular cell layer by oedema, but no other pathological changes were noted apart from two areas of demyelination associated with dense gliosis which were recognized in the fresh brain. In the spinal cord the only abnormalities were an increase in glial nuclei in the anterior horn region with a probable reduction in the number of nerve cells and slight satellitosis. There was no loss of myelin in the lateral columns.

Dr. McMenemey concluded that the changes in the brain were consistent with hypertension and uraemia and that those in the cord, although minimal, would be consistent with early motor neurone disease. However, with the degree of weakness and amyotrophy noted one would have expected a more definite loss of cells. The possibility therefore of these symptoms being due to a toxic effect on the anterior horn cells or on the neuromyal apparatus distal to them, or to a metabolic failure, cannot be excluded.

Pathologist's Diagnosis

(1) Polycystic disease of the kidneys.

(2) Malignant hypertension.

(3) "Hexamethonium lung."

(4) Motor-neurone disease with secondary atrophy of the muscles.

FIG. 11.—An undecalcified section of vertebra showing thick osteoid seams (pale) contrasted with calcified bone (dark). (×100.)

(5) Renal osteodystrophy with osteomalacia and osteitis fibrosa.

(6) Secondary hyperparathyroidism.

(7) Long-standing uraemic pericarditis.

(8) An aneurysm of the membranous part of the interventricular septum.

Discussion

Professor MCMICHAEL: This case has many unusual features amplified by a new form of treatment which may have extended his life by ten years. The first surprise is that he had polycystic kidneys; he had been diagnosed as nephritis on the basis of a progressive renal lesion and the absence of clinical renal enlargement. The condition was atypical in that anatomical enlargement was slight and asymmetrical, and the surface of the kidney was smooth. His malignant hypertension had retinal changes sufficiently severe to impair very seriously his vision. The result of hypotensive treatment was clearing of the retinitis and quite possibly reversal of some of the commonly occurring fibrinoid necrotic and proliferative arteritic changes. Then he had a "hexamethonium lung" which in its early stages shows fibrinous alveolar exudate which went on to healing with fibrotic changes. This must be the first time that this late result has ever been seen. This plastering of the alveolar walls with fibrous tissue extruding into the bronchioles with accompanying giant-cell changes seems to be a new pulmonary lesion. In spite of these extensive changes dyspnoea was never a prominent feature in the later stages of his illness. And then we have the terminal motor-neurone disease. I leave it to Dr. Pallis to say whether this is a coincidence or whether ganglion blockade for ten years was a contributory influence.

MOTOR-NEURONE DISEASE

Dr. PALLIS: The first point about the necropsy was that there were no central neurofibromata, either in the cranial cavity or on any of the posterior roots. We looked for them particularly carefully. The anterior roots were thin, as one would expect in a case of motor-neurone disease. This was most marked in the cervical and lumbar regions. Then we have this most peculiar status spongiosus in several areas of the cerebral cortex. This is not a feature of motor-neurone disease. Taking in conjunction the cerebral status spongiosus found at necropsy, the grossly and persistently raised C.S.F. protein, and the natural evolution of the neurological disorder, with its extremely rapid onset and then virtual arrest, one must conclude, I think, that we are unlikely to be dealing with any of the known variants of motor-neurone disease. The picture suggests, perhaps, some form of toxic motor neuropathy affecting anterior horn cells and cortical neurones. Another point against classical motor-neurone disease is the absence of demyelination in the lateral columns. In motor-neurone disease this is usually found at necropsy even in patients who during life did not show cortico-spinal signs. This patient showed no demyelination in the lateral columns. Perhaps we should call this symptomatic motor-neurone disease. I don't know, however, of what it was symptomatic.

Dr. C. L. COPE: I think Dr. Heard said there was a lot of demyelination—well, there was in the cerebellum.

Dr. PALLIS: The two small areas of demyelination were infarcts.

Dr. COPE: Those are infarcts. They are not associated with any cerebellar symptoms?

Dr. PALLIS: No. Such infarcts are not infrequent underneath the cerebellar folia in patients with malignant hypertension.

Dr. COPE: Isn't it remarkable that they are never associated with signs?

Dr. PALLIS: Small, isolated lesions underneath the folia are quite often found without clinical concomitants. Symptoms or signs would presumably occur if the lesions were larger, more numerous, or involved the cerebellar nuclei or the main efferent pathways.

CENTRAL PULMONARY OEDEMA

Dr. R. E. STEINER: Dr. Heard said, when he described the distribution of the oedema in the lung, that this is classical uraemic oedema: with this I would agree. When we first saw this man the distribution of the oedema was apical, and as far as I could see on histological sections the apices were evidently clear, so there must have been a change in distribution throughout the illness. Could the original oedema not have been due to subacute left ventricular failure, so that we are not only dealing with uraemic oedema but also with the effects of left ventricular failure.

Professor MCMICHAEL: Yes, that was one view. The other fatal cases of hexamethonium lung had left ventricular failure. This man never presented significant failure symptoms. "Uraemic oedema" of the lungs in left ventricular failure is very like early acute lesions of hexamethonium lung.

Dr. HEARD: I am surprised that Dr. Steiner asked this question, because it was his joint paper† that put forward the idea that the left ventricular failure was really the most important thing in these cases.

Dr. STEINER: That's precisely why I am suggesting it.

Dr. J. AZZOPARDI: Isn't hexamethonium lung a misnomer? It's not due to the hexamethonium; it's either a "uraemic" lung, or a "cardiac" lung, or a combination of both.

Dr. HEARD: Well, it doesn't have to be uraemic. Hexamethonium will precipitate it in the absence of uraemia, so hexamethonium does play an important part in its mechanism.

Dr. AZZOPARDI: What happens if you give hexamethonium to a normal person?

Dr. HEARD: I couldn't say.

Professor MCMICHAEL: Well, we've stopped using the drug now, but these lung changes have been described following pentolinium, but not so far as I know with any other hypotensive agents. We had a crop of them eight years ago, and many others running special clinics encountered them. These ganglion-blocking drugs must have had something to do with it, but we just don't understand the mechanism.

Dr. HEARD: I'd like to come back to Dr. Steiner for a moment. He did suggest there was a certain difference between uraemic lungs and left ventricular failure lung. The distribution of the oedema in acute left ventricular failure is just about the same as in uraemia.

Dr. STEINER: If the original exudate was the same at the apices, you would expect a change similar to that seen in the central areas of the lung. This difference suggests that he originally had a less fibrinous oedema which cleared, and the really severe uraemic oedema developed much later and affected the central areas of the lungs. Would you agree to that?

Dr. HEARD: Yes.

Dr. P. HUGH-JONES: Have you any idea what determines the distribution of the oedema? It's a complete mystery to me. Normally the maximum blood flow is at the bases of the lungs, in the upright position, with less in the upper zones. The distribution may even out, as has been shown in left-sided failure, but I cannot quite see why one should have the oedema in this particular distribution in the centre.

Dr. HEARD: I don't think it is understood, though shunts in the pulmonary arterial tree may be responsible. Does Professor Harrison know of any reason for this?

Professor C. V. HARRISON: No.

Dr. STEINER: There's a recent paper by Bergstron *et al.** reporting experiments on dogs where central oedema of the lungs was induced by interfering with the permeability of bronchial arteries. This was very similar to this uraemic oedema in recently induced left ventricular failure; the distribution of the oedema was not central. So it may well be that bronchial artery permeability may in some way affect the distribution.

Professor MCMICHAEL: The only thing that I hang on to is that there are two separate systems of lymphatics, sub-pleural, and peribronchial systems. Central oedema seems to be related to the peribronchial system, spreading out from the roots. Beyond that I have no ideas.

Dr. J. F. GOODWIN: When there has been persistent elevation of pulmonary venous pressure as in mitral stenosis or long-standing left ventricular failure, the medial coats of the pulmonary veins and venules of the lower zones are hypertrophied. This would account for the fact that oedema accumulates in the central core of the lung, where medial hypertrophy of the vessels does not occur to the same extent. At the apices it is even less impressive.

AZOTAEMIC RENAL OSTEODYSTROPHY

Professor MCMICHAEL: Of course the oedema of this man did seem to begin at the apices. Well now, Dr. Milne, will you talk about his renal disorder and its consequences on the bones?

Dr. M. D. MILNE: Well, first of all the diagnosis of polycystic disease: this, of course, would have been easy had we seen the man with a normal blood urea, because I think it would have quite clearly shown on pyelography. However, we only saw him when he was uraemic, pyelography was impossible, and the diagnosis could really only have been made by retrograde, which never seemed to be indicated. I am very pleased we were never asked to do a biopsy on this very tempting large right kidney, otherwise it might have been a rather unpleasant one. Well, I think the bony lesions show very clearly the modern view of what is called, I think properly, azotaemic renal osteodystrophy, this being the osteodystrophy associated with chronic uraemia, and contrasting with the non-azotaemic renal osteodystrophy in renal tubular syndromes. In the latter, the non-azotaemic lesion is a pure unadulterated osteomalacia or rickets according to the age of the patient. In azotaemic renal osteodystrophy, as in this type, there is often, I think, if carefully looked for, a combination of the three classical lesions—secondary hyperparathyroidism manifested by osteoclastic reabsorption of

*Doniach, I., Morrison, B., and Steiner, R. E., *Brit. Heart J.*, 1954, **16**, 101.

†Bergstron, K. E., Ising, U., Linder, E., and Lunderquist, A., *Acta radiol. (Stockh.)*, 1960, **54**, 97.

bone, osteomalacia manifested by wide non-calcified osteoid seams, and uraemic osteosclerosis, which is most marked in the spine usually and which has been aptly described as the "Rugger Jersey" spine by Professor C. E. Dent. This refers to the fact that rugby teams in this country always have horizontal stripes on their jerseys, whereas soccer teams have vertical stripes. You can see that in the part of the vertebra adjacent to the disk the osteosclerosis is usually more severe. I don't know the reason for this.

Now let's consider the aetiology of these bone lesions. The osteitis fibrosa is, I think, certainly due to secondary hyperparathyroidism: here the parathyroids were grossly enlarged. I am not going to speculate on what causes the secondary hyperparathyroidism, however. The osteomalacia is rather unusual in that it is the only osteomalacia associated with a high calcium × phosphorus solubility product; all other types have a low solubility product. The usual explanation is either that there is a toxic factor in uraemic serum preventing deposition of calcium phosphate in the osteoid matrix or that there is a secondary resistance to the action of vitamin D or calciferol. Later on in the course of the disease this osteoid matrix does seem to begin to ossify, and that is the reason for the osteosclerosis and why it occurs particularly in bones with a very rapid turnover, such as the vertebrae, where it is seen most clearly radiologically. The osteodystrophy here is a classical example of modern views of uraemic skeletal disease. Finally there is the question of toxicity of hypotensive drugs. Pentolinium and hexamethonium are usually distributed in the extracellular fluid and do not enter the brain in great concentration. Drugs of the pempidine and mecamylamine class enter the brain very freely and are concentrated in cell nuclei, and I think it would be very interesting to know whether before the development of this extremely atypical motor-neurone disease he did ever receive drugs of the amine hypotensive class rather than the quaternary group which do not enter the central nervous system.

Dr. PALLIS: Dr. Harrington, can you give an answer to this?

Dr. M. HARRINGTON: Up until 1958 he was treated only with hexamethonium and pentolinium. He did have pempidine later, but not until after he developed the neurological changes.

POLYCYSTIC KIDNEY

Dr. AZZOPARDI: Dr. Milne, isn't it unusual to see a case of polycystic kidneys with no family history of hypertension, cerebral haemorrhage, or renal disease?

Dr. MILNE: It is a hereditary disease which continues from generation to generation. The fact that it is a somewhat lethal gene means that mutations do occur, and that he may have been a mutant; on the other hand, unless a patient comes to necropsy this is a disease which may often be missed, and we do not know that his parents did not have it. This man would not have been diagnosed except for the skill and the more easy access of the pathologist's method of examination.

Dr. STEINER: Dr. Milne, you say it is a disease which is often missed and at the same time you say that retrograde pyelography is not really indicated in this condition whilst the patient is in cardiac failure. Nevertheless, should we not carry out retrograde pyelography more frequently?

Dr. MILNE: I would have thought not, because this would not have modified treatment and there is always the risk in retrograde pyelography of introducing infection. It might have been that if we had done this we would have been having the conference in 1954 as a pyelonephritic polycystic kidney instead of now without secondary infection.

Dr. AZZOPARDI: Could Dr. Pallis please tell us whether the E.E.G. findings could be accounted for by the uraemia alone or whether they imply structural cerebral damage?

Dr. PALLIS: We have two E.E.G.s on this patient. The first was taken in September, 1958, when the blood urea was about 240 mg. At that level of blood urea most patients show little alpha rhythm and predominant slower activity. The abnormality found at that stage was probably no more than might have been expected with a considerably raised blood urea. In retrospect, however, and knowing about this status spongiosus of the cerebral grey matter, one might think differently.

ASSOCIATED POLYCYTHAEMIA

Dr. HUGH-JONES: Could I ask Dr. Milne how often in polycystic kidney disease one gets associated polycythaemia? I noticed this particular patient had not got it, but I believe those who work with erythropoietin have come to the conclusion that there is more than just a chance association between these two conditions.

Dr. MILNE: I think it is an impossible question to answer, because everybody who is recording polycythaemia with polycystic kidneys is putting the cases rapidly into medical literature, whereas patients without polycythaemia are not recorded. I don't think at the moment we can answer the question. Few people have a large series of patients with polycystic kidney.

Dr. HUGH-JONES: You have no idea what sort of proportion of cases with polycystic kidneys get polycythaemia?

Dr. MILNE: Well, I take it you tend to get a high and unequivocal polycythaemia in the non-uraemic cases. This man was uraemic throughout and there might have been a secondary anaemia imposed on a primary polycythaemic blood picture.

Dr. C. C. BOOTH: He had a haemoglobin of 84% and his blood urea was ranging from 240 to 297 mg. Isn't this a rather high haemoglobin for that degree of uraemia?

Dr. HUGH-JONES: His haemoglobin was over 90% initially, but it fell to 84% after his uraemia.

Professor MCMICHAEL: Are there many people here who do not know what erythropoietin is? There is a well-established association of certain forms of renal disease, particularly hypernephroma, with polycythaemia. I have regrets that we did not have serial pulmonary function studies on this man. At the onset of his illness we were not well enough equipped, so you see how chances are missed in medicine. One other point I would just like to mention is his organizing pericarditis. Uraemic pericarditis is often a terminal event appearing in the last few days. The nephritic malignant hypertensive tends to live longer than the non-nephritic type, sometimes even for months, and thus allowing time for pericarditis to become organized.

We are grateful to Dr. J. P. Shillingford and Dr. B. E. Heard for assistance in preparing this report, and to the photographic department of the Postgraduate Medical School for the illustrations.

British Medical Association

129TH ANNUAL MEETING AND BIENNIAL CONFERENCE OF THE NEW ZEALAND BRANCH, AUCKLAND, 1961

SUMMARY OF PROCEEDINGS

ROUND-TABLE CONFERENCES

Tuesday, February 7

The Present Position of Steroid Therapy

Dr. W. E. HENLEY (Auckland) was in the chair, and the panel consisted of Professor SHEILA SHERLOCK (London), Dr. W. D. WYLIE (London), Dr. W. S. TEGNER (London), and Dr. H. J. WALLACE (London). Dr. WYLIE (London) began by emphasizing the importance of giving intramuscular cortisone acetate pre-operatively during an operation and post-operatively to patients previously receiving steroid treatment. Adrenal failure must be anticipated for very long periods after cessation of steroid therapy, probably five years, and perhaps even longer. He believed that cortisone had no place in the treatment of surgical shock except possibly in the surgery of the premature infant.

Dr. WALLACE (London) believed that there were only two main indications for systemic steroid therapy in dermatological practice—severe pemphigus and systemic lupus erythematosus with renal involvement. He believed triamcinolone was of low value in the treatment of psoriasis. Its use was not justifiable because of the complications of, firstly, exfoliative dermatitis on withdrawal, and, secondly, the production of widespread septic psoriasis. He did not regard hydrocortisone ointment as contraindicated in infancy, but smaller than usual concentrations were often adequate.

Dr. TEGNER (London) thought that steroid therapy had eased the lot of the rheumatologist and his patient a little, but the risk of hypercorticalism was very real. Temptation to increase dosage if symptoms worsened must be resisted. A barium-meal examination was an essential prerequisite to treatment. Soluble prednisone phosphate therapy might be less commonly associated with peptic ulceration, but this was not yet certain. Intra-articular cortisone was an advantage to some patients, but should not be repeated more than once in six weeks.

Professor SHERLOCK (London) said that in the nephrotic syndrome corticosteroid therapy was rarely needed as a diuretic but should be used as long-term maintenance therapy. Very large doses should be given to patients with systemic lupus erythematosus and renal involvement. Prednisolone should not be given to the average patient with acute virus hepatitis. It was indicated for the fulminant case passing into hepatic coma and for relapses. If the patient showed deepening jaundice for more than four weeks and developed features of obstructive jaundice, he would be "whitewashed" by prednisolone and the duration of illness curtailed.

Summing up, Dr. HENLEY (Auckland) said steroid therapy should be approached in the same way as the state of marriage—"reverently, soberly, advisedly, and in the fear of God."

Thursday, February 9

Ulcerative Colitis

Dr. J. W. BARTRUM (Paeroa) was in the chair, and the panel consisted of Mr. A. LAWRENCE ABEL (London), Mr. G. E. MOLONEY (Oxford), Dr. A. P. MILLAR (Sydney), and Dr. C. ALLAN BIRCH (Enfield, Middlesex). The first questioner asked what proportion of the cases dealt with at hospital would be controlled by medicine and what by surgery. Mr. MOLONEY said that in the United Oxford Hospitals in the last five years about 250 new patients had been brought under control by medical measures, only one patient in this group needing surgery for uncontrolled bleeding from Christmas disease. Old chronic disease was another matter. Mr. ABEL said that, at the Gordon Hospital in London, general medical measures were instituted immediately and then corticosteroids tried for two to three days. If there was no immediate response, surgery was employed, and this surgical group amounted to about 25% of the total. Dr. BIRCH said he had used surgery more than the Oxford workers but not as frequently as those at the Gordon Hospital, and he preferred the longer trial with corticosteroids. In a general discussion on the indications for surgery there was general agreement that in chronic disease with a colon reduced to a functionless, inflamed tube, perhaps with pseudopolyposis and stricture, it was better removed. The possibility of carcinoma arising should only be used as an additional argument for removal in chronic disease after some ten years or more.

Dr. MILLAR reviewed possible aetiological factors and stressed autoimmunity or food allergy as likely causes, especially in view of the disease responding to steroids, and Mr. MOLONEY pointed out the recent findings of Truelove that ulcerative colitis in some cases came or went with or without milk in the diet. As to diet, Mr. ABEL said he favoured apple juice in the first few days, but the other members of the panel preferred a high-protein diet from the start. There was general agreement that steroids should be given in full dosage from the start, and Mr. MOLONEY and Dr. BIRCH agreed that prednisolone by mouth and by enemata (preferably by means of the tube devised by Matts) was the best method of administration, though in severe cases it could be given by intravenous administration. In cases of relapse the same regime could be used or rectal administration only could be tried. One of the great benefits of rectal administration was that, being topical in application, none of the usual complications seen with systemic administration had been observed.

Mr. ABEL outlined the extensive experience of the Gordon Hospital team with ileorectal anastomosis, and stressed the need to avoid the unpleasantness of an ileostomy. Mr. MOLONEY agreed that the operation had a place, but, though without personal experience, he believed that the experiences of others had not been as fortunate as the Gordon team with the operation and that, with extensive disease, ileostomy was usually the most satisfactory long-term measure. Both surgeons agreed that the evidence that steroids might increase the liability to perforation and the surgical difficulties was uncertain, but suggested there might be some truth in this. However, it was more than counterbalanced by the patients who received help from steroids. Mr. Abel showed slides to illustrate some technical details.

Friday, February 10

Thyroid Disease

After explaining that the discussion would first cover tests of thyroid function and then some of the current clinical problems of thyroid disease, the chairman, Mr. K. N. MCNAMARA (Auckland), introduced his panel: Professor T. RUSSELL FRASER (London), who opened the discussion, Dr. H. K. IBBERTSON (Auckland), Professor G. J. FRAENKEL (Dunedin), Professor J. LOEWENTHAL (Sydney), and Professor B. W. WINDEYER (London).

Professor RUSSELL FRASER said that all the iodine taken into the body passed through the thyroid gland, thus offering two points at which radioiodine could measure the gland's activity—first the thyroid uptake of iodine, and secondly the rate of iodine secretion by the gland. There were three main tests of thyroid function—the basal metabolic rate,

the radioiodine test, and the plasma protein-bound iodine. When performed well, each was of approximately equivalent accuracy; but, since each measured a different aspect of thyroid function, they had different limitations and advantages, and the different tests could supplement each other. Dr. IBBERTSON noted that the B.M.R. in many hospitals was really an A.M.R. (agitated M.R.), but it should mean a sleeping M.R.—estimated in well-sedated and prepared patients sleeping during the test. Professor FRASER, agreeing, added that the best screening test was probably by radioiodine. However, Professor WINDEYER pointed out that it might be precluded by previously administered drugs containing iodine-like *x*-ray contrast media, and so the B.M.R. must never be discarded. The plasma protein-bound iodine test was especially useful in detecting almost all thyrotoxic goitres and distinguishing them from avid nontoxic goitres, but it could not recognize myxoedema, and the liver was also high in lymphadenoid goitre. Professor LOEWENTHAL said that partial hypothyroidism was difficult to recognize, but it might be revealed by the effect on the plasma cholesterol and E.C.G. of administering 0.1 mg. of L-thyroxine per day for two weeks. Dr. IBBERTSON noted the usefulness of recording tendon jerks to discern subthyroid subjects, and the value of assessing clinical impressions by the use of the "Wayne Index," but warned against any reliance on it in atypical cases. He also mentioned the usefulness of two supplementary radioiodine tests, especially useful in patients already given antithyroid drugs—the triiodothyronine suppression test and the iodide repletion test.

Treatment of Thyrotoxicosis

Professor FRAENKEL discussed the treatment of thyrotoxicosis. He found operative treatment best for all nodular goitres and for many thyrotoxic diffuse goitres. Professor WINDEYER noted that radioiodine was the preferred treatment for patients aged over 45 years, and led to no risk of leukaemia. Mr. MCNAMARA, summarizing, found all treatments useful for some conditions, surgery being especially so for young adults and those with large goitres.

Professor LOEWENTHAL thought that the clinically solitary nodule—rarely found—was best removed, in the same way as a lump in the breast. But Dr. IBBERTSON found that scanning identified "hot" ones which could be treated medically. The surgeons agreed that thyroid biopsy was having increasing uses; and Professor FRASER showed a high-speed biopsy drill. To the final question of what function the thyroid served came two answers—to give zest for living (Professor Fraser) and to enhance the beauty of a damsel's neck (Dr. Ibbertson).

THE SECTIONS

SECTION OF GENERAL PRACTICE

Tuesday, February 7

Family Life and Medicine in the U.S.S.R.

With Dr. D. C. CAMPBELL (Auckland) in the chair, Dr. J. H. HUNT (London) gave a talk, illustrated by coloured transparencies, on his visit last year to the U.S.S.R.—a visit made at the request of the *Sunday Times*, for which paper Dr. Hunt wrote a series of articles on his return to England. He went as a private individual without sponsorship by the British Government or invitation from the Soviet Government. Indeed, before he left for Russia it seemed very unlikely that he would be able to do more than a few of the tasks he had set himself to achieve. These included visits to Soviet practitioners in their homes and their places of work in many different parts of the U.S.S.R., attendance at their office consultations, visits to their patients, seeing out-patient clinics, travelling in ambulances and in the planes of the flying-doctor service. He spent six weeks in the U.S.S.R., and travelled in Russia, the Ukraine, and the Caucasus, and over to the Mongolian border. He took over 700 photographs. In five weeks he travelled 10,000 miles, but found a surprising amount of similarity, almost standardization, among the doctors, their homes, and their equipment, in widely separated parts of the Union.

Accommodation was still cramped, and few doctors (no matter the size of their families) had more than a three-roomed flat. The general standard of medicine was good. Preventive measures had eliminated typhus, plague, and relapsing fever, and there was now little cholera, smallpox, or leprosy. Ninety-five per cent. of family doctors at present were women. Throughout the U.S.S.R. there was one doctor (of all types) to 450 people: 75% of all these doctors were women. This percentage might change in the future, for in the intake, now, of medical students the numbers of men and women were approximately equal.

The prestige of the doctor was high. Working hours were limited to six and a half hours a day. Medical training was provided free to students, but once qualified they were expected to serve their first three years in one of the more remote country areas. After this they usually returned to a city for further hospital experience. In the country areas —where the population was sufficient—the doctors worked in groups of about eight, and the group cared for 2,500 to 3,000 people.

There were five grades of doctors, the doctor rising with ability, experience, and seniority through these grades. Even inside the grades there were distinction awards (a 25% increase of pay) for some 20% in each grade. Postgraduate study was encouraged, and every four years six months' paid study leave was allowed. Each doctor had a nurse as assistant, and was provided by the State with a car and driver. Most investigations were carried out in policlinics, but it was possible to have *x*-ray and E.C.G. examinations made in the patient's home with portable apparatus.

Dr. Hunt's many photographs gave a very vivid insight into the home and working conditions of the Soviet doctor and his or her patient. He was thanked by Dr. Campbell for his lucid talk and for the easy and witty way he had presented his material.

Undergraduate and Postgraduate Education

A forum of undergraduate and postgraduate Education Committees of the New Zealand Faculties of the College of General Practitioners, held under the chairmanship of Dr. T. D. C. CHILDS (Auckland), was addressed by Dr. J. H. HUNT (London) and Dr. E. C. MCCOY (Vancouver). Dr. HUNT spoke about general practice and undergraduate education in Great Britain. He said that the deans of medical schools were finding an increasing demand among students for training oriented towards general practice. General practice should be regarded as a different approach to general medicine rather than as a different subject. He considered that the undergraduate training for general practice went on after qualification until the young doctor became established in general practice, and that his postgraduate education began then and needed to continue through his life as a practitioner. He listed ways in which the training of the doctor for general practice could and should be influenced. These included: the co-option of G.P.s to student selection boards, lectures to undergraduates by selected G.P.s, student attachment to G.P.s, the use of training notes prepared by the College for the G.P. trainer and trainee, G.P. advisers to study boards (helping even with examinations, if required), attendance of students at domiciliary visits in consultation with specialists, and vacation exchange schemes like that started by the Montefiore Hospital in New York.

Dr. C. L. E. L. SHEPPARD (Canterbury Faculty) spoke about the need for longer post-qualification training before a graduate entered independent general practice. He was in favour of a period of two to three years' provisional registration, during which time the new graduate should be required to undertake a stipulated series of house appointments. Dr. R. H. BOWIE (Wellington Faculty) thought this difficulty was largely solved by the trainee practitioner scheme in England.

Dr. A. TALBOT ROGERS (South-east England Faculty) said that with the relative increase in vacancies in assistantships and partnerships the number of young doctors seeking to spend a year as a trainee practitioner was falling. He said also that in Britain difficulties had been found in establishing rotating internships, and that there was considerable resistance on the part of the newly qualified to having the compulsory pre-registration year extended in any way. Dr. JOHN HUNT said that he agreed it was not desirable that the period of compulsory house appointments before registration should be increased, but the College of General Practitioners could well encourage longer postgraduate training in suitable special posts in hospital, by making this a prerequisite for taking its own higher diplomas when those were established.

Canadian Experience

Dr. E. C. MCCOY (Vancouver) said that postgraduate education was the crux of the work of the College of General Practitioners in Canada. They required of their members that each should undertake 100 hours of such study every two years. Of these hours, 50 should be spent in a formal approved course (usually planned by a university and lasting from three days to three weeks). At least 15 hours should be spent in attending the scientific sections of annual meetings; the remainder could be informal—this included attendance at local clinical meetings, hospital rounds, work on tape recordings, or correspondence courses. In Canada they were strict in their requirements, and if it became clear that a member was not fulfilling the obligations to pursue his postgraduate study his name was removed from membership of the College.

To enable members to fulfil their obligations the Canadian College was helping in the provision of greater opportunities for postgraduate study, and among other schemes had, with university co-operation and the financial assistance of two drug firms, recently established scholarships enabling G.P.s to spend three weeks working in a university teaching hospital under the direct supervision of a tutor who guided his studies, and obtained for him access to any hospital unit in which he wished particularly to study. A questionary to the Canadian College ascertained that most G.P.s in Canada thought a period of three or four years' postgraduate experience was desirable before entering general practice.

Dr. L. H. CORDERY (Christchurch) pointed out that geographically New Zealand doctors were handicapped, as overseas postgraduate training involved heavy expense in time and money. He favoured a sabbatical year for study overseas every five years, with some form of State grant to help the general practitioner to achieve this. Dr. D. C. CAMPBELL (Auckland) was doubtful whether the toughness of Canada over termination of membership was often possible in New Zealand. It was difficult often to know how much good work a man was doing. Affidavits had been suggested, but the suggestion had not been well received, and was most resisted by the members who were the very ones on whose studies reliable information was needed. Dr. MCCOY believed that unless the College was prepared to be tough and to make examples of defaulters, no general raising of effort and achievement was likely to ensue.

SECTIONS OF GENERAL PRACTICE AND ANAESTHESIA

Tuesday, February 7

Artificial Respiration

With the vice-president of the Section of General Practice, Dr. C. L. E. L. SHEPPARD (Christchurch), in the chair, Dr. W. R. LANG (Auckland) opened the discussion by reviewing the present ideas on the physiology of the lung and respiration. Most of the present knowledge on drowning had come from experimental work on dogs, and because of the lack of detailed laboratory studies in human beings it had been difficult to be sure that what happened in experiments on the dog actually happened in the human. However, from the data collected over the years a fairly clear-cut picture was tending to emerge. The basic work had been done by G. Swan, of Texas, and now Halmagyi and Cobbatch had added further observations in the past year.

It appeared that the response of the body differed in fresh-water drowning from that in sea water, though the initial stage was the same. This initial stage consisted of breath-holding, lowering of oxygen tension, and then inhalation of fluid followed by intense glottic spasm with resultant asphyxia. In fresh-water drowning the water was quickly absorbed from the lungs to cause haemodilution. The only blood constituent not lowered was potassium, which might rise to 8 mEq/litre as haemolysis occurred. Pulmonary oedema then set in, and the blood constituents moved into the intrapulmonary spaces, where they were churned up into a frothy fluid by respiratory efforts.

The heart went into ventricular fibrillation, and the blood-pressure fell precipitously. This all occurred within two to three minutes of immersion. On the other hand, with sea-water drowning the electrolytic imbalance was in the reverse direction. Diffusion of salts occurred with explosive speed, causing a great elevation of plasma sodium, chloride, and magnesium levels. This gave a picture of haemoconcentration. Fulminating pulmonary oedema was then precipitated, but there was no ventricular fibrillation, and the heart might continue to function for up to nine minutes before the blood-pressure fell and the heart came to rest in diastole. It had been found that oxygen under pressure was a better resuscitator than air under both these circumstances.

Dr. W. J. WATT (Auckland) then reviewed methods of artificial respiration. He stressed the fact that, apart from the asphyxial element, there were the serious osmotic effects in drowning that had been mentioned.

He said that the New Zealand Society of Anaesthetists had been asked to assist the Standing Committee of Resuscitation of the Health Department, and they had finally recommended that the mouth-to-mouth technique, giving a positive-pressure inflation of the lungs, was the most effective one.

In all the techniques described over the past 100 years there was the difficulty of maintaining an adequate airway. Though people, such as Silvester, had modified techniques to obtain a clearer airway, it really needed two people to try to carry out these techniques satisfactorily—one to keep the airway clear and the other to do the manual work of expanding the chest. In the mouth-to-mouth technique the operator could keep the airway clear and at the same time inflate the lungs. It was a difficult method to teach, but with modern films and the excellent manikin now available he felt that it should be advocated. Elam of the U.S.A. and Ruben of Copenhagen had suggested mouth-to-mouth respiration, but Dr. Watt felt that obstruction of the nose lessened the free passage of air; with the new-style airway, which most of the resuscitation teams now had in Auckland, mouth-to-mouth ventilation with positive inflation of the lungs was the method of choice.

SECTION OF ANAESTHESIA

Tuesday, February 7

Systemic Disease and Anaesthesia

With the vice-president, Dr. G. F. V. ANSON (Auckland), in the chair, Dr. W. D. WYLIE (London), the president of the Section of Anaesthesia, spoke on "Systemic Disease and Anaesthesia." He pointed out that surgical patients often suffered from a disease in a system of the body other than that associated with the operative condition. The commonest systems which were at fault were the cardiovascular and respiratory mechanisms of the patient. Despite the introduction of numerous diagnostic and function tests the

pre-operative assessment and calculation of true risk was still very much a personal opinion.

It appeared from a series reported by Dana and Ohler in 1956 that patients with healed cardiac infarction showed an operative mortality of 7.4%, whereas fit patients undergoing similar operations had a mortality of 1.4%. On the other hand, patients with symptomless disease were a greater risk under anaesthesia, and Sharpey-Schafer and Taylor had shown that many normal diabetic patients had absent or partially absent circulatory reflexes, a fact which must be borne in mind when assessing patients. At the same time, fear might be sufficiently profound to lead to fainting during induction or recovery from anaesthesia, as Bourne had shown.

As to the respiratory system, Dr. Wylie felt that much of the pre-operative measurement of respiratory function carried out these days was unsatisfactory to the clinical anaesthetist, as it did not help to determine which patients would be satisfactory on controlled respiration and which would be better on spontaneous respiration. Unfortunately, cardiac and respiratory disease usually went hand in hand, so that assessment was doubly difficult, but the anaesthetist must know whether he would be able to inflate the lungs. There was a case to be made for giving a test dose of thiopentone together with one of the short-acting relaxant agents and measuring the resistance to inflation before the patients came to surgery, so as to be in a position to know what was going to happen at operation.

In an analysis of patients going through the recovery room at St. Thomas's Hospital, it was seen that the majority who stayed over 30 minutes were there because of either cardiovascular or respiratory difficulties which were attributable to the anaesthesia. The only way to ease these difficulties was by complete co-operation between physician, surgeon, and anaesthetist, and by the anaesthetist paying more than one visit to the patient in the pre-operative phase.

Dr. A. N. SLATER (Wellington), Dr. T. MAGNER (Auckland), and Dr. R. M. B. PENHEAROW (Gisborne) in a discussion afterwards asked what technique was to be employed in the cases of respiratory difficulty mentioned. Dr. WYLIE said there was a strong case to be put forward for the use of local, spinal, and epidural anaesthesia. Dr. MAGNER (Auckland) asked whether Dr. Wylie felt that respiratory function tests were more useful than careful blood-gas analysis, to which Dr. WYLIE replied that neither provided a really clear-cut picture. Dr. J. R. McN. HOUSTON (Browns Bay) asked if there was any method to assess the lack of vasomotor control in patients. Dr. WYLIE replied that he was not aware of any method at the present time.

Thursday, February 9

Deaths Associated with Anaesthesia

With the president, Dr. W. D. WYLIE (London), in the chair, Dr. J. R. RITCHIE (Dunedin) opened the discussion on deaths associated with anaesthesia. He pointed out that the New Zealand Society of Anaesthetists had developed about seven years previously an anonymous system of recording cases of deaths in which anaesthesia had been involved. This had been done not to attribute blame but to find out what improvements could be made in techniques and teaching. Consequently recorders had been set up in various centres throughout New Zealand, and he had acted as central recorder.

The cause of death had been broken down into four groups: first, where death was due to an obvious defect in anaesthetic technique; secondly, where the upset in normal physiology due to anaesthesia was too much for a patient whose physiology was already altered by disease; thirdly, where the cause of death was unknown but could be guessed; fourthly, where the death was not due to the anaesthetic in any way. Another fact in classification was the fitness of the patient before operation, and for this they had used the old international risk terminology of A, B, C, D, qualifying with the letter E for emergencies. He felt that this system was not very accurate and allowed for different interpretations. However, it had allowed him to grade cases. At the same time, he appealed for the setting up of an international coding system so that results could be compared in different parts of the world.

In the six years that he had under review only 95 cases had been recorded, whereas in the years 1948–56 there had been 379 coroner's cases of deaths associated with anaesthesia. He therefore felt that recorders were not co-operating as well as they should. Breaking the two sets of records down, he found that in the first series of 95 there were only 45 cases which should be considered. Of these, the anaesthetic was shown to be definitely responsible in three, largely responsible in three, partly responsible in four, and only slightly responsible in 35. In the second series of 379 cases he found that 90 were unavoidable, the majority were only slightly avoidable, whereas 130 appeared to be avoidable and were due to faults in technique or inadequate resuscitation. As a final comment Dr. Ritchie thought a worth-while improvement could be if one could eliminate the unexplained deaths occurring in young children at the end of an apparently straightforward anaesthetic.

Dr. W. J. PRYOR (Christchurch) said that the position of coroner's cases in New Zealand was different from that in Great Britain, but from unofficial talks that he had had he understood that before long the position in New Zealand would be similar, so that comparison from that point of view might be easier in the future. In 1956 the Association of Anaesthetists in Great Britain had reported on 1,000 cases. An important point they had stressed was that in the great majority there had been a departure from accepted techniques, and this should be brought to the attention of those responsible for the teaching of anaesthetics. The Beecher and Todd study of 600,000 cases from 10 teaching hospitals showed that one case in every 2,680 was due to the anaesthetic alone, and that in one case in 1,560 the anaesthetic was an important factor. In the Canterbury area in the past six years he had collected 29 cases of death associated with anaesthesia; there he found that 20 could be said to be due to anaesthetic or probable anaesthetic cause, and if he broke the series of 20 down further he found that in 15 of those cases death could have been prevented. He felt that this was a salutary thought, but if something could be learnt from past mistakes the goal of *in somno securitas* would ultimately be reached.

In discussion Dr. ANNIE W. WALL (Adelaide) stressed the absolute need for anonymous recording, as they had had trouble nearly leading to litigation over this matter. Dr. J. S. CHURCH (New Plymouth) entered a plea for people to be more frank in discussion before a coroner's inquest, so that details could be recorded before they went from mind. Dr. J. F. MCCULLOCH (Sydney) felt that many deaths reported in children could be avoided if care was taken to avoid too deep ether anaesthesia and to look out for insidious loss of blood.

SECTION OF OPHTHALMOLOGY

Tuesday, February 7

Contact Lenses

With the president of the Section, Mr. FRANK LAW, in the chair, Mr. G. DE L. FENWICK (Auckland) read a paper on the present position of contact lenses. He surveyed the different types of contact lens and the indications for their use. The method of fitting micro-lenses was then illustrated, and they were discussed under the following headings: (*a*) statistical results—intolerance, effect of lens on cornea, causes of failure; (*b*) price—circumstances in which lenses were obtainable through social security, etc. In the discussion which followed, Mr. LAW said he agreed with the speaker that the estimate of the value of micro-lenses which he had received from Mr. F. Ridley in London—that very few were worn and that they were liable to cause corneal abrasions and ulcers—was not his experience. He thought that they were becoming increasingly popular. In answer to Dr. I. K. WILSON (Wanganui) Mr. FENWICK said

that the lenses were marked to avoid confusion of right with left. He agreed with Mr. G. G. TALBOT (Auckland) that they were most useful in uniocular aphakia, though it was rare for binocular vision to be restored. Dr. R. H. LINDO FERGUSON (Auckland) asked if these patients had to wear two lenses for comfort, one being afocal, but Mr. FENWICK said that this was not so.

Dr. C. A. PITTAR (Auckland) asked about bifocal contact lenses. Mr. FENWICK said that he had had little experience of these and thought that they would not be very satisfactory; they would have to be unrotatable. Dr. C. C. RING (Auckland) asked the cost of a single lens, and also about the attitude of the authorities towards free supply under social security. He was informed that a single lens cost £20. Dr. R. G. S. FERGUSON (Wellington) said that lenses were available under social security for approved conditions such as conical cornea, high myopia, and uniocular aphakia. Dr. M. R. ASHBRIDGE (Wellington) said that even if binocular vision was not achieved in uniocular aphakia the increase in field justified the fitting of a contact lens.

Ophthalmologists, Opticians, and National Health in Great Britain

In the afternoon, with Mr. H. V. COVERDALE (Auckland) in the chair, Mr. FRANK LAW reviewed the situation in Great Britain regarding ophthalmologists, opticians, and national health. He opened by referring to his paper on "Ophthalmology in Great Britain under the National Health Service" which had appeared in the *Transactions of the Ophthalmological Society of Australia* for 1949. His predictions had received striking confirmation in the remarks of the immediate Past-President of the British Medical Association at Torquay. He gave an analytical review of 85,000 cases seen in the Supplementary Ophthalmic Service, and pointed out the difference between the number of cases from that service which were referred back to their general practitioners by opticians and by ophthalmic medical practitioners, respectively, on account of pathological conditions, which he classified. He then described the development of the National Health Service, and compared actuality with anticipation and prediction, referring especially to the relationship in Great Britain between ophthalmologists and opticians. He indicated the number of staff of each type employed in the hospital eye service.

Mr. Law then described the events leading up to the passing of the Act for the registration of opticians, and the formation and constitution of the General Optical Council, of which he was one of the six medical members. Over 6,000 ophthalmic opticians were already on the *Register*, 876 dispensing opticians, and 816 bodies corporate. The council had been very active, for, besides compiling the *Register*, it had found and equipped premises, formulated rules, set up many committees, and dealt with financial and disciplinary matters. An important aspect of its present activity concerned the opticians' responsibilities and restrictions in the practice of orthoptics, the use of drugs, and the fitting of contact lenses. On the question of giving of clinical experience to newly qualified opticians in hospital, a matter that was at present being discussed between the General Optical Council and the Faculty, Mr. Law said the outcome might well be influenced by the poor response which had been accorded to the scheme for employing opticians in hospitals as refractionists. He recorded the reports of two opticians from New Zealand who had recently visited the United Kingdom to study present conditions, and concluded with a summary of the state of optical legislation in many parts of the world, adding that he thought that the outcome of the negotiations of the past years were likely to be satisfactory, resulting in no detriment to the professional and financial welfare of the ophthalmic medical practitioner, but consolidating the status of the ophthalmic optician while controlling his activities and eliminating the provision of glasses by the unqualified.

The chairman said that it was valuable to hear this description of the situation in the United Kingdom. In reply to Dr. G. DE L. FENWICK (Auckland) Mr. LAW said that at present it was still possible for unqualified people to fit contact lenses. Dr. C. C. RING (Auckland) asked about the number of opticians working as refractionists in hospital. Mr. LAW replied that they were very few, probably because of the low rates of pay offered. Mr. G. G. TALBOT (Auckland) said that the relative figures Mr. Law had given of the numbers of patients referred to hospital by opticians and by ophthalmic medical practitioners respectively differed little from those published by Mr. Bishop Harman in the 1920's. Mr. L. W. POOLE (Auckland) wondered how the diagnoses had been collected by the speaker. He was advised that these had only been given in detail from the ophthalmic medical practitioners' references.

Microphthalmos

The paper on microphthalmos by Mr. J. BRUCE HAMILTON (Hobart) was read in his absence by Dr. CHARLES SWANSTON (Auckland). In his paper Mr. HAMILTON said that the chief cause of microphthalmos appeared to be intrauterine infection. He discussed the effect of rubella and its mutations on the intrauterine development of the eyes, and offered some speculations on the mode of mutation of the virus. A review of toxoplasmic choroido-retinitis and encephalomyelitis showed this disease to be a frequent factor in microphthalmos. The speaker discussed the state of the placenta in toxoplasmosis and reviewed the treatment of both rubella and toxoplasmosis, recounting three recent cases. Finally he considered the differential diagnosis of microphthalmos and the role of cytomegalic inclusion disease in its production.

COMBINED SECTIONS OF ORTHOPAEDICS AND RADIOLOGY

Tuesday, February 7

Spinal Osteoporosis

With Dr. THOMAS LODGE (Sheffield) in the chair, Mr. H. JACKSON BURROWS (London) read a paper on spinal osteoporosis. He recalled that osteoporosis, or increased porosity of bone, represented an imbalance between bone formation and bone removal. This balance could be upset by disuse or by involutional or hormonal disturbances. The modern fashion of confining the term to deficient bone formation was wrong; in disuse osteoporosis, for instance, it was almost certain that excessive bone removal was the more important factor. On the other hand, a distinotion from osteomalacia was important. Post-menopausal osteoporosis had little meaning, even when extended to men.

In spinal osteoporosis the rarefaction involved bones with red marrow—spine, thorax, and limb girdles—and was sometimes generalized. The pelvic deformities of osteomalacia were not found in osteoporosis, nor (except in cortisone porosis) pseudofractures; bone tenderness was uncommon. The vertebrae, especially lumbar, yielded, becoming biconcave; thoracic vertebrae might become wedged, and an occasional vertebra might show frank collapse. Thoracic kyphosis was seen, but lumbar lordosis was uncommon because involvement of the vertebrae as a whole caused telescoping or loss of height, as witness approximation of the spinous processes. The end-plates of hyaline cartilage became very greatly thinned and also impressed.

The habitus of the patient reflected these changes with consequent abdominal protuberance, supra-abdominal grooves in front and subcostal grooves dorsally. Shortening of the spine might be recorded by a comparison of the measurement from vertex to symphysis pubis with that from symphysis to sole and with the half span. Backache was of gradual onset, worse on exertion, and relieved by

rest; and might radiate ventrally or distally. In about half the cases an acute crisis of vertebral collapse might be initiated by a trivial act, driving the patient to bed, afraid and unable to move.

Differential Diagnosis

The differential diagnosis was mainly from other porotic diseases of bone—Cushing's syndrome, hypopituitarism, hyperparathyroidism among the hormonal diseases, and the marrow diseases, leukaemias, some anaemias (including sickle-cell anaemia), Gaucher's disease, myelomatosis, lymphadenoma, and carcinomatosis. The speaker described and illustrated, in connexion with the differential diagnosis, a case of osteomalacia in a woman of 66. After a total cystectomy and formation of a rectal bladder her tenth thoracic vertebra collapsed, and treatment by androgens and oestrogens on the assumption that the condition was osteoporosis failed to improve her. Later a gross chloride retention was found, consequent upon reabsorption from the rectal urinary contents. She was put on a salt-free diet and was restored to reasonably good health and activity.

Exclusion of conditions that might simulate osteoporosis required not only full clinical and radiographic investigation but also haemoglobin estimation, blood cytology, E.S.R., Wassermann reaction, serum calcium and phosphorus, phosphatase, alkali reserve, blood proteins, urine for Bence Jones protein, faecal fat, sternal puncture, and bone biopsy. With the exception of bone biopsy the results of all these tests might be expected to be normal in uncomplicated osteoporosis as here understood, unless the alkaline phosphatase were raised from a recent vertebral fracture. The patient should not be confined to bed, as recumbency promoted disuse porosis. Although anabolic steroids would often correct the mineral loss, so also, surprisingly, would an increased mineral intake; the clinical and chemical improvements were not accompanied by appreciable radiological improvement. Though the speaker referred mainly to florid cases, there were minor and early examples which might escape attention. Among these, mild cases of Cushing's syndrome should be suspected if hypertension was present.

Discussion

In discussion, Dr. THOMAS LODGE asked Mr. Jackson Burrows the relationship of osteoporosis to neurogenic factors as encountered in traumatic paraplegia. This appeared to be confined in paraplegics to the point in the spine below the site of the lesion. Mr. JACKSON BURROWS said he thought there were two causal factors here: one was ordinary disuse in the paralytic patient, and the second was the necessary immobilization causing decalcification and the formation of ureteric stones. Dr. LODGE also asked about the incidents in cases of slipping vertebrae where osteoporotic changes appeared to be more localized. Mr. JACKSON BURROWS thought that this was almost certainly mechanical, but it could not truly be answered on a mechanical basis because the changes did not always occur where they were expected.

Mr. A. F. DWYER (Sydney) asked if Mr. Jackson Burrows meant the ordinary removal or absorption of bone by osteoporosis or was it a more active process; to which Mr. BURROWS replied that this depended on the number of lacunae involved rather than the presence of osteoclasts. Mr. DWYER asked about the expansion of the disk body and whether this was due to lack of compression force in the vertebrae or whether there was some other factor as well. Mr. JACKSON BURROWS thought that there must be some other factor as well. It was not readily explainable.

Mr. W. PARKE (Gisborne) thought that the speaker had been most modest, and had not made any mention of much original work which he himself had done on the subject. Mr. Parke also asked how was one to manage the elderly person in acute pain from one or more collapses of vertebral bodies when it was not advised that they should be put to bed. Mr. JACKSON BURROWS agreed that this was a most difficult problem, but there were two avenues of help. One was in the form of supports, corseting, and braces, by the Fisher jacket, if the patient would wear them. The second was by suitable medication, which was even more important than the support, in the form of steroids, calcium, and phosphorus. There was, of course, the difficult period between the application of medication and the response to treatment.

Dr. COLIN J. ALEXANDER (Auckland) asked Mr. Jackson Burrows if he could offer any explanation for the appearance of florid callus formation round the fractures which occurred in Cushing's syndrome and which was typical of that condition whereas no such callus formed in ordinary osteoporosis. No explanation could be offered.

Control of Bone Growth

Dr. B. W. A. LEEMING (Wellington) read a paper on control of bone growth. He said that in man, at least, maturation of bone was really a combination of two separate factors, and bone development consisted in three distinct processes, each under a different hormonal control. Asling and Evans, from carefully controlled experiments in rats, some of which had had pituitary ablation, some thyroidectomy, and some both procedures, had concluded that growth hormone caused growth in length but had no effect on maturation. Thyroxine caused maturation and had some effect on bone growth. When growth hormone was given with thyroxine the rate of growth was greater than when either was given alone. This work suggested that bone growth and bone maturation were under separate endocrine control, at least in the rat.

In humans the most striking evidence was derived from over-activity and under-activity of the pituitary. Prepubertal over-activity promoted gigantism with delayed epiphysial union with continuing growth in length, while in pituitary infantilism there was a deficiency of growth hormone and an absence of testicular and other hormones. Again the epiphyses failed to unite at puberty, but there was little or no growth in skeletal length, and the patient might fail to reach a height above 30 in. (75 cm.). Growth hormone alone was not entirely responsible for skeletal height, nor could epiphysial closure be exclusively attributed to the androgens. Some synergistic action was probable.

Ovarian Agenesis

The speaker had carried out a radiological estimation of the bone ages of 75 patients with ovarian agenesis, mostly examples of Turner's syndrome. Radiographs of the hand and wrist were available in 25 patients and of the pelvis in 21. The whole group, with one exception, were registered as females. The criteria of bone-age assessment in the hand radiographs were those of Greulich and Pyle. Hand lengths were measured from the radiographs and plotted against normal standards. In ovarian agenesis the bone age correlated closely with the chronological age until 12 or 13 years; it then remained static for some years, and about the 20th year the epiphyses united and the skeletal and chronological ages then corresponded.

In normal children there was a regular increase in hand length which did not cease at the 13th year. The graph of the patients with ovarian agenesis showed the same curve but at a lower level. These children grew at a normal rate, but at any age they were somewhat shorter than normal. The balance between bone growth and maturation was disturbed. The stimulus responsible for bone maturation was functioning, but that responsible for epiphysial fusion was lacking, so the abnormality could be explained in terms of the dissociation theory of bone growth and maturation. It was not easy to decide which hormone or group of hormones controlled each component: all the patients had a low oestrogen output, but the 17-ketosteroid level was also low, and if the latter could be regarded as a crude index of blood androgen it suggested a reduced adrenal androgen output. The blood level of growth hormone in these patients was presumed to be normal. In 18 cases the pelvic inlet was of the android type. This was deduced

from films of the pelvis taken during excretion urography, it having first been decided from a sex estimation in normals that such a pelvic radiograph was reliable.

The high proportion of male-type pelves could not be due to excess androgen output, as the androgen blood-level was probably low. In the absence of oestrogenic stimulation the probability was that the pelvic inlet remained in its prepubertal form. In the female the lack of stimulation of epiphysial closure was probably a reflection of the absence of circulating oestrogens. This introduced a further control of skeletal growth. Maturation was under the control of thyroxine, growth under that of growth hormone, and epiphysial closure (in the female) under that of oestrogenic substances. In ovarian agenesis the normal maturation was due to normal thyroxine blood-levels.

Professor RUSSELL FRASER (London) suggested that abnormal chromosomes (e.g., XO females) might have some significance in connexion with the lower total growth and might be more important than the hormonal effect. Skeletal sensitivity might be seen only at 12 years of age, and thyroid still had an effect on maturation after puberty.

SECTION OF OTOLARYNGOLOGY

Tuesday, February 7

Maxillary Sinusitis

With the vice-president of the Section, Mr. E. I. A. MACDONALD (Auckland), in the chair, Mr. MYLES FORMBY (London) read a paper on maxillary sinusitis. He said that a knowledge of the physiology of the nose and pathology of the mucous membrane of the sinuses was essential for a proper understanding of the principles of treatment. He described nasal physiology under four headings: (1) air currents; (2) capillary blood flow; (3) cilia; (4) mucus. The well-recognized catarrhal type of patient susceptible to frequent and prolonged colds was most likely to suffer from sinusitis. Mr. Formby stressed the aetiological role of viruses and allergy as well as bacteria and dental sepsis.

Allergy might be considered under three categories: (1) uncomplicated; (2) allergy with superimposed infection; (3) primary virus infection, the symptoms of which could so resemble those of allergy as to be impossible to differentiate.

Sinusitis was primarily a disease of the mucous membrane; if the bone became involved that was a complication. As a result of infection the changes occurring in the mucous membrane might result in (*a*) the filling or partial filling of the antrum with exudate, and (*b*) cyst development in the mucous membrane. These cysts were important, as they might contain not only serous fluid but also often thick pus. This condition was often the cause of failure in conservative treatment. Radiography was of great value in diagnosis. Mr. Formby said that the aim in treatment was to give maximum assistance to nature and the patient's own resistance. Outside diseases should be corrected and anatomical defects should receive attention. Antibiotics were essential in acute disease and prevented post-operative complications; but they interfered with the development of the patient's own immunity. Retained fluid should be treated by puncture and lavage. In children, indwelling polyethylene tubes were very convenient. Ventilation of the sinus was important, and allergy and dental infection should be treated. Displacement could be used. For reduction of the enlarged inferior turbinals he preferred sclerosing injection of sodium morrhuate to cautery or diathermy.

Operation became necessary for: (1) failure of conservative treatment; (2) cysts or polypi; (3) oro-orbital fistula; (4) malignant disease. He advised the radical Caldwell–Luc operation and considered there was no place for the simple intranasal antrostomy.

Opening the discussion, Mr. A. A. MACGIBBON (Palmerston North) asked what experience Mr. Formby had had in treating sinusitis with ultrasonic waves. In reply, Mr. FORMBY said that he considered the treatment valueless, as they would be absorbed before reaching the sinus. Mr. A. BROGAN (Sydney) asked the speaker to describe his method of retaining the polyethylene tubes. Mr. FORMBY replied that he used silk transfusion thread anchored to strapping on the nose. Dr. K. B. HALLAM (Christchurch) asked if the speaker had any experience of rebound phenomena after using decongestants. Mr. FORMBY replied that in his experience "fenox" was particularly liable to cause these effects. Mr. T. G. SWINBURNE (Melbourne) asked for reasons for Mr. Formby's statement that virus infection could mimic allergy. Mr. FORMBY replied that simple lavage of sinuses which proved to contain no bacteria was often effective in curing the patient. Classical allergic changes were sometimes unilateral and could be cured by the Caldwell–Luc operation, and no evidence could be found of bacterial infection. Mr. R. A. ELLIOTT (Wellington) asked Mr. Formby for his experience of using steroids. Mr. FORMBY replied that he thought their effect was temporary and did not recommend their prolonged use. Mr. R. G. PHILLIPS-TURNER (Hamilton) described his experience of the value of alcohol in the treatment of sinusitis.

SECTION OF RHEUMATOLOGY

Tuesday, February 7

Reiter's Disease

With Dr. A. ROWATT BROWN (Auckland) in the chair, Dr. W. S. TEGNER (London) presented a paper on Reiter's disease. He said that recent work on Reiter's disease had done much to clarify the condition itself and to establish its place among the arthritides. Its history was of great interest, for a search into the literature showed that it seemed to have been accurately described more than 100 years ago by Benjamin Brodie. The first symptoms varied greatly, as the feet, the eyes, the joints, or the genital tract might produce the first complaints. It was probably comparatively common in the male, but rare in the female. Probably the commonest way in which the condition presented was with pain in the heels and feet and coexistent urethritis and conjunctivitis. The latter might have to be inquired for specifically. Diarrhoea also might occur.

Case histories were then described by Dr. Tegner. He said that differential diagnosis involved distinguishing the condition from gonorrhoea, ankylosing spondylitis, and rheumatoid arthritis. The differentiation from gonorrhoea was of great historical interest. The two conditions probably frequently coexisted. It was necessary to revise many ideas held about gonoccocal arthritis and such conditions as keratoderma blennorrhagica.

The aetiology was unknown. The question whether the condition was venereally or otherwise acquired remained doubtful. It was presumed to be due to a viral infection. In investigating the condition, the history, the physical examination, radiology, and an examination of the prostate were all important. Treatment was largely symptomatic, but antibiotics seemed to help clear up the prostatitis. The prognosis was on the whole good, but relapses might occur.

Dr. B. S. ROSE (Rotorua) asked if gold salts were of use in the treatment of Reiter's disease.

Dr. F. DUDLEY HART (London) stated that in most cases the disorder was self-limiting, and long-term therapy of this kind was not called for. In cases with skin changes one was loath to use a form of treatment in which skin reactions were among the commoner toxic reaction.

Dr. J. MOORE TWEED (Wellington) said that in the past there had been confusion between Reiter's disease and gonococcal arthritis, particularly as both conditions might coexist. Reiter's disease was, however, usually clinically distinct from rheumatoid arthritis or gonococcal arthritis, though very similar in some cases of ankylosing spondylitis and the arthritis associated with colitis or proctitis. In such a self-limiting disease he considered the judicious use of steroids entirely reasonable.

Dr. J. M. TWHIGG (Wellington), like Benjamin Brodie 120 years earlier, had given colchicum in some cases and thought that favourable results were sometimes seen.

Dr. F. DUDLEY HART (London) said that after the war ex-Service patients with acute arthritis of feet and ankles due to Reiter's disease, often if not usually acquired as a venereal disease, were drawing pensions for it. Though the disease was usually clinically distinct, the pattern of Reiter's disease was not appreciated sufficiently at that time. He had seen a case in a girl who ten years later had died with an aortic lesion identical with that seen in ankylosing spondylitis.

Dr. MICHAEL KELLY (Melbourne) pointed out that, though Benjamin Brodie had described Reiter's disease very adequately in 1818, Dr. Musgrave, of Exeter, had referred to a non-venereal arthritis as long ago as 1702.

Patterns of Rheumatism in New Zealand

With Dr. WILLIAM S. TEGNER in the chair, Dr. B. S. ROSE (Rotorua) reported with Dr. I. C. ISDALE (Rotorua) on patterns of rheumatism in New Zealand.

They reviewed the history of the present knowledge of rheumatism in the Maori, and the present prevalence compared with that in the local European population. The Maori suffered more from gout and rheumatic fever, but less from rheumatoid arthritis. The relative aetiological importance of genetic and environmental factors was discussed, with particular reference to secretor status, blood groups, cultural differences, social conditions, nutrition, and infection. Sufficient evidence was presented to justify further attention to environmental factors in prevention and management. Further study of genetic factors was indicated.

Phenylbutazone and Immobilization in the Treatment of Arthritis

Dr. M. KELLY (Melbourne) said that phenylbutazone was not a general analgesic or anti-inflammatory agent. It was the first specifically antirheumatic drug, unique in its effect on rheumatic inflammatory lesions. It was safe if the contraindications were observed, the daily dose did not exceed 400 mg., and it was withdrawn as soon as undesirable symptoms appeared. It was cumulative, and intermittent treatment was best, with maintenance doses as low as possible. Relapses were due to an unresponsive state which could be overcome by stopping medication for a few days and starting again. In severe and crippling arthritis of hands and knees relapses could be avoided with the aid of splinting. Perseverance was required to get the best value from it; treatment should never be abandoned merely because the patient had had a relapse. Suppositories might be good for patients who got dyspepsia. With the methods described, and with G.27202 for unresponsive subjects, the proportion of patients who could be treated safely had steadily increased during nine years. It should never be necessary to treat rheumatic patients with steroids.

Dr. ADAH PLATTS-MILLS (Auckland) asked why cardiac disease was considered to be a contraindication to the use of phenylbutazone. Dr. KELLY replied that he had seen patients in such cases deteriorate rapidly on the treatment, and he considered active cardiac disease an absolute contraindication to treatment with phenylbutazone.

Dr. I. C. ISDALE (Rotorua) had found, like Dr. Kelly, that phenylbutazone was a useful drug in the treatment of gout, a condition which was common in the Maori population. He had found phenylbutazone and colchicum a useful combination in those cases where colchicum alone proved unsatisfactory.

Dr. I. S. DE B. BROADFOOT (Auckland) asked what treatment was required for the toxic effects of the drug. Dr. KELLY replied that withdrawal of the drug was the only practical measure.

In answer to a question from Dr. J. W. BARTRUM (Paeroa) regarding skin reaction to the drug, Dr. KELLY replied that such reactions might take almost any form, often resembling, for instance, rubella. On withdrawal of the drug the skin reaction gradually faded, though it might worsen for a day or two subsequently.

SECTION OF MEDICINE

Thursday, February 9

Advances in the Treatment of Liver Disease

Under the chairmanship of Professor RUSSELL FRASER (London), Professor SHEILA SHERLOCK (London) outlined recent advances in the treatment of liver disease. She said that corticosteroid therapy was indicated in active cirrhosis with jaundice and high serum globulin levels. In spite of clinical and biochemical improvement, serial liver biopsy sections showed little change. Bleeding from oesophageal varices could usually be controlled by intravenous vasopressin injections. Porto-caval shunt operations should be reserved for young people with good liver function, but even in these patients chronic neuropsychiatric changes occurring post-operatively were common. Hepatic coma was often precipitated by some additional factor such as haemorrhage, diuretics, narcotics, or infection; neomycin therapy was essential. Ascites in most instances could be controlled by rigid restriction of dietary sodium and chlorothiazide with potassium supplements. Spironolactone should be added if necessary. Complications of diuretic therapy included hypokalaemia, hyponatraemia, and hepatic coma.

Answering Dr. A. H. ROBERTSON (Brisbane), Professor SHERLOCK said that large quantities of spironolactone might be required, even up to 1,200 mg. daily in some instances. Mannitol given intravenously could be used as an osmotic (water) diuretic in particularly resistant cases.

Professor RUSSELL FRASER (London) observed that small doses of prednisolone might have a large effect in patients with liver disease, who were unable to detoxicate the steroid. Corticosteroids could be safely given to pregnant women with hepatitis if it was indicated.

Dr. D. W. BEAVEN (Christchurch) had observed haemolysis in some patients with cirrhosis, and speculated on the effect of prednisolone therapy. Professor SHERLOCK said that Dr. R. S. Williams at the Royal Free Hospital, London, had found decreased red-cell survival in all forms of liver disease. This was unaffected by steroid therapy and might be due to a defect in the red blood cell itself. The occasional patient with a positive Coombs test did well with steroids.

Dr. E. K. HUGHES (Auckland) questioned the current period of bed-rest for patients with hepatitis. Professor SHERLOCK said that, though early ambulation might be allowed in patients in hospital, it was wise to keep domiciliary patients in bed until they were symptom-free and jaundice-free and the liver was no longer tender.

COMBINED SECTIONS OF SURGERY AND CARDIOTHORACIC SURGERY

Thursday, February 9

Hiatus Hernia

With Professor P. J. MOIR (Leeds) in the chair, Mr. A. DICKSON WRIGHT opened the discussion. Large hernias through the diaphragm, he said, might persist for many years without causing symptoms. By contrast, hiatal hernias might be small and difficult to demonstrate, yet caused severe symptoms. Those caused by reflux were much the most important. The diaphragm itself was not an effective sphincter of the cardia, for the fingers were not gripped by it during light anaesthesia. The hiatal orifice was directed backwards, not upwards. Pregnancy and obesity increased abdominal pressure and promoted hernia.

The gut had a number of sphincters—pharyngeal, pyloric, ileo-caecal, anal—and Mr. Dickson Wright was sure there

was also an intrinsic one at the lower end of the gullet. If it went wrong in one way, cardiospasm resulted; if in another, reflux. The sling of the crus could in no way be compared to the levator ani, which was an intelligent muscle. The action of the crus was esoteric. He thought the phreno-oesophageal ligament illusory. A patient could be cured of his hiatal hernia and still have his symptoms. He preferred the abdominal approach, and resected the oesophagus only when it was a complete wreck. A cat got cardiospasm if its vagi were cut, and so he always cut the vagi in man to stimulate the sphincter. He anchored the oesophagus in the middle of the hiatus, and sewed the fundus to the under-surface of the diaphragm, carrying out a gastroenterostomy when a duodenal ulcer was present, as it often was. He also removed any gall-stones. Harrington was a chest surgeon, and he also preferred the abdominal route. Thoracic surgeons did this operation through the chest only in order to stake a claim on the disease. He had not tried it, but thought Boerema's technique, in which the stomach was fixed to the anterior abdominal wall, best.

Mr. GEOFFREY FLAVELL (London) said he disagreed with most of the things Mr. Dickson Wright had said. They were there not to promote absurd rivalries but to decide which route was best. Para-oesophageal hernias were not those in which fundus rolled up beside the gullet on the left, but were always congenital, always in preformed sacs, and always in the right of the gullet. Such large hernias produced an important symptom—breathlessness. He knew of no convincing evidence of an intrinsic sphincter, and the matter had been debated inconclusively since 1715. The important part played by the right crus was to keep and increase the angulation between gullet and fundus. He quoted and illustrated the work of Paul Morand to this effect.

Medical treatment had little to offer in hiatus hernia. 30% had oesophagitis and bleeding, 10% developed strictures. The latter could be more troublesome to treat than carcinomas and ought never to be dilated before reflux was corrected. Ulceration was an urgent indication for repair, which always led to healing and often relief of dysphagia. The argument in favour of the thoracic approach was simple and unanswerable. It was an axiom of surgery that sutures must not be placed under tension, and this was even more stringently so in hernia surgery. To reduce many of these hernias and suture them in place without tension, especially those with much inflammation, it was often necessary to mobilize the gullet up to the aortic arch. No one could do this through the abdomen. The proof of the pudding was in the eating, and the consequences of placing sutures under tension were demonstrated in the respective recurrence rates of abdominal and thoracic surgeons. He hoped Mr. Dickson Wright would allow that, by and large, they were equally honest. Harrington and all the other laparotomists had some 40% of unrelieved patients. With the operation done through the chest the recurrence rate was 4% and over 80% of patients were relieved of their symptoms.

Mr. Flavell presented a personal series of 112 cases, with one death from coronary thrombosis three days post-operatively and four recurrences. He illustrated his technique, which avoided opening the diaphragm or interfering in any way with the phrenic nerve.

Sir DOUGLAS ROBB (Auckland) discussed hiatus hernia in infancy. In most cases symptoms could be traced to the first year of life. These hernias were undoubtedly the commonest variety of congenital diaphragmatic hernia. Bleeding from them came later than the first week, and radiological confirmation later still. They were often presented as a "feeding problem" and were also confused with pyloric stenosis. Most underwent spontaneous cure, but stricture formation was apt to be early. About 35% were not improved by weaning and some 5% developed strictures. He preferred the thoracic route for the reasons given by Mr. Flavell. He had operated upon 37, 24 male and 13 female. Simple repairs (with two repeats) were done in 27, and major resections of strictures in 10. The great majority had been presented during the first year of life. In the 27 simple transthoracic repairs results were excellent in 18, good in 7, and there had been one recurrence which had been repaired. One died of hyperpyrexia post-operatively. Of the 10 resections, one had been a Roux loop, one a jejunal implant, and seven oesophago-gastrostomies, two of these being above the aortic arch. Six of the patients were finally well, four had died of later complications, two of them from strangulation through the hiatus.

Mr. W. M. MACLAURIN (Auckland), Mr. RICHARD ORGIAS (Wellington), who preferred the abdominal route because he had found it easier and quicker, and Mr. G. E. MOLONEY (Oxford), who wondered if vagotomy alone were not sufficient, without bothering to reduce the hernia, took part in the discussion.

91st HUNTERIAN ORATION

SIR RUSSELL BROCK ON RESEARCH

The 91st Hunterian Oration was delivered by Sir RUSSELL BROCK before the Royal College of Surgeons of England on Tuesday, February 14. Taking as his theme the museum, research, and the inspiration of Hunter, Sir Russell Brock said that adulation of Hunter's museum was ill-conceived in relation to the grand plan of Hunter's life and work. His museum, being the expression of the results of his observations and research, must be subservient to his research, and it was that element of his life and work that should be more admired and followed.

Present Vocational Emphasis

In the present policy towards research it must be recognized that there were many who did not wish to be research workers. They wanted, quite rightly, to be practical physicians or surgeons, good doctors, or good teachers. At the same time there were many who might develop an interest in research and who could make lasting contributions were they aided by opportunity and example. At present few students and trainees were influenced actively towards research, and there was certainly a great temptation for the surgeon to deflect from research. That must be resisted if the Hunterian tradition were to be honoured. There could be no denying that from at least the early years of this century the position of research in training programmes in this country had become quite different from that in the American scheme of training. Many thought that there it had reached excess; but one could not ignore the fact that the opportunity, the stimulus, the facilities, and also the inspiration were there. In Great Britain by far the greater emphasis had been on the vocational side. More lip-service had been paid to research than actual encouragement and direction given. This country had bred many excellent, practical surgeons—probably the best in the world; like, however, begot like, and, as the main emphasis in so many centres had been on a routine training, young men were encouraged—possibly subconsciously—to follow on primarily in that. They were led to think that vocational training came first, and, although they might rub shoulders with research, they were liable to think that it was the exceptional type who indulged in it.

The research urge should be a living integral part of the work and life. Certainly it was so in Hunter's environment. At present a registrar might fear to interrupt his clinical training to take a research post. The reverse should be the case. He should be encouraged to do so—not compelled, for not all are that way inclined; but the opportunity should be deliberately offered for him to refuse if he wished. Even though he made no useful discovery, the spell of training in the methods and disciplines of research could profit both him and his patients. Every school should have a registrar

establishment large enough to allow at least one man to be seconded into a research post for one to two years. "If this had been so during the last half-century we could have produced more original work than we have done and could have received less spoon-feeding from others," continued Sir Russell.

New Department of Surgical Science

Happily things were now altering and more and more was being done in many centres throughout the country. The academic departments of the universities contributed their portion to research, but they had the distractions of administration and of undergraduate teaching. In so far as the grand plan of surgery throughout England, and indeed throughout much of the Commonwealth, was concerned, it was the College which should play a leading role. It had been decided that the College's present research activities, large though they be, must be completed by the establishment of a Department of Surgical Science with a professor at its head. The proposed new chair of surgical science would differ from the usual university chair in that the professor would be spared the distractions of routine teaching and of departmental administration. He would be able to devote his full time to his own investigations and also to directing and training young surgeons in the experimental and scientific approach to surgery. He should be the catalyst in the policy that sought to direct more young men into scientific as opposed to purely vocational surgery.

In advocating the scientific approach to surgery, Sir Russell said he would not like it to be thought that he deprecated the vocational approach. He had tried to point out that important advance by way of it was bound to be limited. That was because the horizon of purely vocational achievement was discernible, was commonly limited to the immediate technical problems, and did not include fundamentals. A vocational method of training usually resulted in the habit of waiting for someone else to make the next step forward, of accepting spoon-feeding from others as the usual method of improvement. The inquiring mind which could work through scientific methods and training knew no fixed horizon.

Part-time Research

There were many who enjoyed the ordinary practice of surgery and would abandon it with reluctance for an entirely academic life, continued Sir Russell Brock. In fact, strong arguments could be put forward against a totally academic training in surgery. There was little doubt that an academic life could be lived within horizons just as fixed and dull as those of a purely vocational life, especially if initiative were blunted by security and by too much routine administration. It was easy to be complacent and to feel that the provision of full-time academic posts would ensure continuing advance, and there was a danger of that in Britain to-day. It was often desirable that the academic worker should meet the problems of clinical practice which could inspire thoughts and ideas for progress. It was for that reason that he was personally disturbed by too much insistence on a big expansion of whole-time posts. Much good work could still be contributed by the part-time academic worker. The policy should be to encourage those men who wished to combine clinical practice and research by providing more posts for them. It had been the custom for a new consultant to receive four or five weekly sessions at his main hospital, and in order to fill his time and earn a living he had to seek odd appointments in other hospitals. "How much better would it be if, with proper safeguards, he could employ his remaining sessions in a research post within his main hospital."

Subjects for Research

The young man seeking a problem for research often asked what he should choose. To him so much seemed settled or proved. That was one of the weaknesses of the vocational or apprenticeship method of teaching, much of which had to be didactic. The answer was—almost anything and everything. There was scarcely any aspect or department of knowledge which could not benefit from re-scrutiny or re-examination. What the young man needed was not so much a field in which to research, but encouragement, guidance, and financing within that field. "Our young man also needs the encouragement of inspiration," concluded Sir Russell Brock. "This alone can elevate and impel forwards. This should be the very spirit of the College. This is what we should learn to-day from our contemplation of Hunter's life."

Nova et Vetera

DR. FRANCIS ADAMS OF BANCHORY

DIED FEBRUARY 26, 1861

A century has passed since Francis Adams, a leading classical scholar of his time, died at his home in Banchory, on Deeside, where he had laboured as a well-loved country doctor for more than 40 years. Laborious years they were, because, besides meeting the demands of a wide and exacting practice, he translated, for publication by the Sydenham Society, a number of Greek medical classics which were still in demand as textbooks.

The son of a gardener at Lumphanan, in Kincardineshire, he had taken the degree of M.A. at Aberdeen University and had studied medicine in London, where he became M.R.C.S. in 1815. He then returned north to settle in Banchory (or Banchory-Ternan), and there he spent the remainder of his life, receiving well-merited honours from Aberdeen (M.D.) and Oxford (LL.D.) Universities, but declining the invitation to become professor of Greek at Aberdeen, preferring to minister to the needs of his patients, although this involved many a long ride on horseback.

How he found time for the practice, the translations, and the duty of guiding the destinies of his six children left motherless at an early age remains a mystery to us to-day. It was indeed an arduous life, and he confessed that he accomplished all his tasks only by the curtailment of his hours of sleep. He worked late and rose early, and thus was he able to translate the seven books of Paul of Aegina (his hardest task), the works of Aretaeus of Alexandria, and (most important of all) the *Genuine Works of Hippocrates* of Cos, which, since 460 B.C., have had a profound effect on the advance of medical knowledge.

The generation of medical men to which Francis Adams belonged was the last to practise medicine according to the old-standing Hippocratic tradition. During his lifetime, surgical anaesthesia came into being, and there was much talk of the "germ theory" in medical circles, but Lister had not yet revolutionized surgery by his discovery of the antiseptic principle.

The classic works which Adams translated were about to suffer eclipse as the newer knowledge became available. Nevertheless, they remain as a landmark, as suggestive works which are still worth reading, and as a memorial to one of the most able practitioners of Victorian days. In an obituary notice in the *Scotsman*, which was reprinted in the charming collection of essays entitled "Horae Subsecivae," Dr. John Brown acclaimed Francis Adams as the leading scholar of his time, and it is only fitting that we, a hundred years later, should add our tribute of thanks to the Hippocrates of Deeside.

DOUGLAS GUTHRIE.

To-day's Drugs

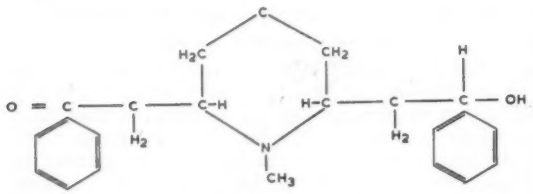
With the help of expert contributors we publish below notes on a selection of drugs in current use.

Lobeline

Lobeline injection B.N.F.

"Lobidan" (Uni-pharma).

Chemistry.—α-Lobeline is the chief alkaloid of Indian tobacco (*Lobelia inflata*). It is a piperidine derivative and has the following structural formula:



Pharmacology.—The actions of lobeline are similar to those of nicotine, but it is less potent. The main effects are on the carotid body and the autonomic ganglia, but lobeline also stimulates pain and cough receptors in the pleura and axon reflexes that cause sweating. It has additional stimulant effects on skeletal muscle.

Therapy.—In clinical medicine the main use of lobeline has been as a respiratory stimulant. Injections of pure lobeline (3–10 mg. intramuscularly) are used traditionally to stimulate respiration in newborn babies and less commonly in adults with emphysema. Crude extracts of the herb are frequently found as constituents of proprietary cough mixtures. The respiratory stimulation is due mainly to the action of lobeline on the carotid sinus mechanism. It has been shown that the action is exclusively on the chemoreceptors but that the site of action is central to that of both oxygen lack and carbon-dioxide excess.[1] Thus lobeline may be effective in patients who are already anoxic and have a raised carbon-dioxide content in the plasma. In clinical practice, however, the action of lobeline is found to be somewhat unpredictable and very transient. It is therefore not considered a worth-while respiratory stimulant, and either leptazol or nikethamide are more reliable drugs for this purpose.

The other purpose for which lobeline may be used stems from its resemblance to nicotine. It has been suggested that the use of lobeline may help the nicotine addict who genuinely wishes to stop smoking to overcome his craving. Recently a proprietary preparation (lobidan) containing lobeline and a mixture of rapid- and slow-acting gastric antacids has become available in Great Britain. A short-term clinical trial[2] in the U.S.A. suggested that this preparation was of immediate help in assisting people who were really anxious to stop smoking. At the end of one month, however, the proportion of those who had used the lobeline preparation and were still not smoking was only 53%, and it is doubtful if this result is any better than might have been achieved by firm encouragement.

Side-effects.—The side-effects are similar to those of nicotine, and will be familiar to anyone who remembers his first experiences with smoking. Addiction is said not to occur, but in view of the similarity with nicotine it seems possible that anyone who took a smoking deterrent containing lobeline for more than a short period might transfer his addiction from nicotine to lobeline.

N.H.S. Basic Price.—Lobidan tabs., 15 for 10s. 5d.

REFERENCES

1 Liljestrand, G., *Brit. med. J.*, 1951, **2**, 623.

2 Rapp, G. S., and Olen, A. A., *Amer. J. med. Sci.*, 1955, **230**, 9.

Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

Registration of Causes of Stillbirth

SIR,—Causes of stillbirth have been registered in England and Wales since October 1, 1960. I would be grateful if you would allow me to comment on one particular aspect of the first three months' results which is causing some concern. During this period, out of a total of 3,737 stillbirths registered, the certificate was given by a doctor in only 2,360, or 63% of cases. In the remaining 37% the certificate was given by a midwife. The proportion is very little different for births at home or in hospital.

It is possible that some doctors may not be aware of the requirements of the Population (Statistics) Act, 1960, which makes it obligatory on every medical practitioner who was either present at the birth of a stillborn child, or who examined the body of such a child, to give a certificate which includes a statement of the cause of death. Only if no doctor was present or examined the body may the certificate be given by a midwife.

The Registrar-General for Scotland has reported[1] that in that country midwives complete stillbirth certificates in only 0.6% of cases.—I am, etc.,

M. A. HEASMAN,
Acting Chief Medical Statistician,
General Register Office.

London W.C.2.

REFERENCE

1 *Annual Report of the Registrar-General for Scotland, 1959*, 1960, p. 55. H.M.S.O., Edinburgh.

1961 Influenza Pattern

SIR,—The outbreak of clinical influenza this year first appeared in this practice in isolated cases between January 4 and 7. The practice population is in a mainly residential area some three miles to the west of Warrington (an industrial town in S.W. Lancashire) and is mostly composed of social classes II, III, and IV (Registrar-General's classification). To the north, west, and south there is open country; in the farming population of the practice no cases of influenza have yet been seen. Clinically the condition has presented in one of two forms: (*a*) Acute upper-respiratory-tract symptoms, with moderate frontal and/or occipital cephalgia, malaise, rigors, coryza, in the first 48 hours: this is followed by the development of an irritant, non-productive tracheal cough with substernal pain. At this stage most of the patients examined have marked and typical intense injection of the anterior pillar of the fauces and soft palate, with corresponding injection of the posterior pharyngeal wall. Some patients have had more severe prostration with continuing pyrexia and anorexia. Constipation is common. (*b*) Alternatively the patient has given a history of nausea for a few hours (often while still taking a normal meal) followed by sudden and marked vomiting lasting up to 24 hours. The vomitus is very yellow. Prostration, rigors, and general muscular pains in torso and limbs have followed. Many of these patients have had an associated acute enteric dysfunction with frequent loose stools for some 24–48 hours. The acute phase usually subsides within 2–3 days, general weakness following.

In most cases one or other of the two types has been seen, but occasionally patients presenting with symptoms affecting primarily one system have developed minor symptoms affecting the other system. In a few patients with more severe affection of the respiratory tract advantage has been taken of the domiciliary radiological diagnostic service: two cases of influenzal pneumonitis and one case of (?) carcinoma bronchus at the right hilum have been demonstrated by this means. Recovery, estimated by the patient's desire to return to work, has taken between two and three weeks in the more severely affected individual.

By use of the Disease Index[1] it has proved possible to maintain a factual record of the incidence of influenza in this practice. In the 14 days January 22 to February 4 the attendance rate for all patients for all complaints (including both surgery and home attendance) has increased by 250% over the recorded annual average for January. Using the College of General Practitioners' Classification of Disease,[2] and basing the practice population on the Age–Sex Register as at December 31, 1960, the Tables below have been constructed. (In this practice population there are slightly more children under age 15, and slightly fewer older persons aged 60 and over, than in the national average given in the National Morbidity Study.[3]) The manifestations of influenza are protean, hence the choice of the relevant diagnostic term is often one of semantics. Seven of the clinical conditions described in the College Classification have been chosen, thus covering almost all the possibilities in presentation and recording.

TABLE I.—*Males: Incidence per* 1,000 *Practice List, by Age-group and Diagnosis*

College Classification No.	Clinical Condition	Age-group						
		-10	-20	-30	-40	-50	-60	60 Plus
81	Acute pharyngitis, nasopharyngitis, coryza ..	12	33	102	38	35	—	12
83	Tonsillitis (non-S.F.*)	—	14	—	—	6	—	—
84	Influenza ..	—	—	16	32	29	16	—
85	Pneumonia, pneumonitis	—	—	—	—	—	16	—
86	Acute bronchitis ..	92	—	—	—	—	25	12
87	Chronic bronchitis	—	—	—	5	—	42	24
8801	Laryngitis, tracheitis	—	—	—	5	—	—	—

TABLE II.—*Females: Incidence per* 1,000 *Practice List, by Age-group and Diagnosis*

College Classification No.	Clinical Condition	Age-group						
		-10	-20	-30	-40	-50	-60	60 Plus
81	Acute pharyngitis, nasopharyngitis, coryza ..	—	32	71	32	29	—	—
83	Tonsillitis (non-S.F.*)	—	19	—	11	—	—	—
84	Influenza ..	—	—	19	6	29	26	15
85	Pneumonia, pneumonitis	—	—	—	—	—	—	8
86	Acute bronchitis ..	76	—	—	—	—	—	8
87	Chronic bronchitis	—	—	—	—	—	—	8
8801	Laryngitis, tracheitis	6	—	13	6	29	—	—

* Non-S.F. = non-scarlet-fever.

Examination of the figures shows that the incidence of "influenza" is between one-third and one-half that of "coryza," and that the more severe condition is found in patients over the age of 20; in both sexes more influenza was diagnosed in the 40–50 age group than in any other. On the other hand, the majority of patients with simple coryza is found in the young adult age group. This may be no more than a manifestation of the fact that the younger and potentially healthier section of the population is more easily able to contend with the infection, and is therefore not apparently so likely to be diagnosed as true influenza. The illness in children under 10 years of age has been grouped simply into those with minor upper-respiratory-tract infection and those presenting with lower-respiratory-tract infection—the latter group are recorded under 86, Acute Bronchitis. The group 87, Chronic Bronchitis, has been included to show the effect of sudden exacerbation of the chronic illness in a patient otherwise quiescent at the time of survey; it is considered that many of the patients in this group may be exhibiting in their own fashion the prevalence of influenza at the moment.—I am, etc.,

Penketh, Lancs. TEVIOT S. EIMERL.

REFERENCES

1 Eimerl, T. S., *J. Coll. gen. Pract.*, 1960, **3**, 246.
2 Classification of Disease, ibid., 1959, **2**, 140.
3 Logan, W. P. D., and Cushion, A. A., *General Register Office. Studies on Medical and Population Subjects*, No. 14, 1958. H.M.S.O., London.

Upright Position in Anaesthesia

SIR,—While agreeing with Dr. J. G. Bourne (January 28, p. 289) that "the main danger with nitrous oxide in dentistry is fainting," we wish to protest most strongly against the statement, "The nigger in the woodpile is the upright position of the subject, and I believe that fainting will be a danger in dental practice with any anaesthetic so long as we continue to give the anaesthetic with the patient sitting up."

In Sweden, adenoidectomy alone is a much commoner operation than the combined tonsillectomy and adenoidectomy. During the year 1959, 30,000 adenoidectomies were performed in Sweden, on children between the ages of 2 and 12, of whom 23,400 were in the upright position.[1] The complications, which were few, consisted of bleeding in seven cases and pneumonia in four, figures which compare favourably with those from other centres. Fainting was conspicuous by its absence, not appearing once in the 23,400 cases.

While this does not solve the problem of the most suitable anaesthetic agent in dental practice, the upright position should not be unjustly condemned.—We are, etc.,

University Hospital, Uppsala, Sweden. BASIL FINER. JAN STAHLE.

REFERENCE

1 Finer, B., and Stahle, J., *Nordisk Medicin*, 1961, to be published.

Brucella Puzzles

SIR,—Your annotation "Brucella Puzzles" (January 28, p. 267) is calculated to arouse in our bosoms the guilty feeling that we are constantly missing cases of an infection so often authoritatively stated to be vastly more prevalent than we suppose. But what is the unfortunate clinician to do? For many years past I have asked for agglutination tests for *Brucella* to be done in any suggestive case of P.U.O., and, considering that a percentage of normal sera are said to agglutinate *Brucella* up to 1/50, one might expect the occasional positive result to leaven the monotonously negative reports. But such expectations have always been disappointed.

What is the cause of this? Is the disease perhaps not so common after all? Has pasteurization eradicated it, at least in urban areas? And there are other considerations. Spink[1] in his exhaustive and admirable monograph suggests that some of the antigens employed may be at fault. Then there are the blocking antibodies, to which you refer, as well as the remarkable prozone phenomenon (by which a serum may be positive 1/1,000 and negative (1/10). Indeed, agglutinins may be absent even when brucellae can be cultured from the blood. Moreover, a high positive titre may persist long after the infection has been extinguished. All in all, then, it is clear that *Brucella* is very unwilling to conform to the accepted canons of immunology, and the agglutination test is a very uncertain indicator of its presence. That drives us back on blood- or marrow-culture, an elaborate and tricky procedure which one is reluctant to impose on one's hard-worked laboratory colleagues unless absolutely necessary.

One further point: Bruce originally discovered *melitensis* as the cause of Malta fever in the soldiers and sailors of the garrison, among whom it was ten times more common than among the Maltese, long accustomed to drinking raw goats' milk. An analysis of Spink's protocols of 244 cases suggests that in the U.S.A. the disease is largely an occupational one, confined to farm workers, veterinary surgeons, slaughter-house men, and those who handle infected carcasses and hides. As in both the U.S.A. and the United Kingdom *abortus* infection in cattle is reputedly widespread, it is remarkable that disease arising from the consumption of raw milk is not much more common than reported. Can it be that, thanks to our age-long parasitism on the cow and her milk, we have become as tolerant of *abortus* as the Maltese of *melitensis*, so that only exceptionally heavy infections will now induce a reaction?—I am, etc.,

South Middlesex Hospital, Isleworth, Middlesex. G. E. BREEN.

REFERENCE

[1] Spink, Wesley W., *The Nature of Brucellosis*, 1956. University of Minnesota Press, Minneapolis.

Mental Hospital Admissions

SIR,—Your readers may be interested in the pattern of admission to a psychiatric hospital during the first three months of the implementation of the Mental Health Act (November 1, 1960, to January 31, 1961). The figures of direct admissions to the Park Prewett Hospital Group were as follows:

Informal	188
Section 29 (up to 72 hours' observation)	76
Section 25 (up to 28 days' observation)	41
Section 26	10
Part V (Sections 60, 65, and 72)	4
Section 136 (admission by constable, up to 72 hours)	2
Total	321

It will be noted that 133 (41.5%) were admitted by compulsion, but only six of these had to be detained after a varying observation period by the use of Section 26; together with the ten admitted in the first instance under Section 26, only 16 (5%) of the total admissions required detention. The others became informal or were discharged. It has not been found necessary on any occasion to use Section 48 (barring discharge by a relative) or Sections 36 and 134 (withholding correspondence to or from patients).—I am, etc.,

Park Prewett Hospital, Basingstoke, Hampshire. I. ATKIN.

Prognosis after Hemiplegia

SIR,—The paper by Dr. G. F. Adams and Mr. J. D. Merrett (February 4, p. 309) gives a dismal outlook for hemiplegic patients, but is very interesting. I am certain much could be done for patients who survive the first few weeks by expert selection for rehabilitation. In this new medical rehabilitation centre of the North-east Metropolitan Regional Board, since the opening ten months ago, 38 patients with hemiplegias have been treated, in addition to other disabled patients. Of these, nine are back at work, 12 are completely independent but not at work, 12 need a little help with dressing, etc., but are able to do most things for themselves, and five are relatively helpless. These patients have been followed up after three months from discharge from here, and their further progress will be observed.

These figures are encouraging, although from a selected group, and confirm the work of Rusk and others.—I am, etc.,

Passmore Edwards House, Rehabilitation Centre, Clacton-on-Sea. J. B. MILLARD.

Jejunal Biopsy

SIR,—The subject of jejunal biopsy has become a topical one (see the paper by Dr. R. H. Girdwood and his associates, February 4, p. 319). Though the terminology of the malabsorption disorders remains unsatisfactory, and though the relationship between the commoner varieties of this syndrome to one another remains obscure, yet there seems to be a general awakening upon the functions of the intestinal villi and the obvious parts they must play in the absorption of fats, proteids, and undoubtedly also of other elements in the diet. Since the technique of jejunal biopsy has been improved by Shiner, and since the introduction of the biopsy capsule by W. H. Crosby and H. W. Kugler[1] in Washington, great advances have been made and there appears to be general agreement on the changes which take place in the villi and which appear to be responsible for failure of their proper functions. These are represented by a flat mucosal surface and abnormally shaped, short, and stumpy villi. The prototype of the malabsorption syndrome is undoubtedly tropical sprue. It was from a study of this well-marked tropical disease that the term "sprue syndrome" was originally derived.

Though my original work on tropical sprue was done long before intestinal biopsy had been thought of, I continue to be very interested in the results which have been obtained by this method; still more so, there is a sense of gratification that my description and figure of the pathological picture of the small intestine in tropical sprue is similar to that described in this paper, and that was 49 years ago. The description I gave of the deformities in the villi[2] remained unconfirmed and therefore were not referred to by subsequent writers on this subject. It has therefore been a source of inward satisfaction that Colonel W. H. Crosby and his American colleagues have unreservedly given me the credit of the original discovery.—I am, etc.,

London W.1. PHILIP MANSON-BAHR.

REFERENCES

[1] Crosby, W. H., and Kugler, H. W., *Tropical Sprue. Studies of the U.S. Army's Sprue Team in Puerto Rico*, 1958, p. 217. Medical Science Publication No. 5.

[2] Bahr, P. H., *A Report on Researches on Sprue in Ceylon 1912–1914*, 1915. Cambridge University Press, London.

ABO Groups in Africans with Peptic Ulcer

SIR,—Professor Ian Aird and his colleagues[1] have shown that in England peptic ulceration occurs more commonly in those people who possess Group O blood. It was postulated by these workers that all blood-group mucopolysaccharides may provide some protection against peptic ulcer, but A and B protect more effectively than O.

Peptic ulceration is frequent among the African population in Nairobi, and it was thought that it would be of interest to ascertain whether this protective effect was apparent in a primitive community. All cases consisted of patients submitted to surgery in King George VI Hospital during the years of 1957–9 either for cure of their ulcer or for the treatment of complications. Patients comprised three tribal groups—Wakikuyu and Wakamba (Bantu) and Jaluo (Nilotic). These tribes

Blood Group	Number of:		Percentage of:	
	Patients with Peptic Ulcers	Persons in General Population	Patients with Peptic Ulcers	Persons in General Population
O	27	1,913	73	50
A	5	971	14	25
B	2	798	5	21
AB	3	143	8	4
Total ..	37	3,825	100	100

constitute the main African population of Nairobi and its environs, the Wakikuyu being in the majority. As the numbers were small all cases were grouped together for statistical analysis. There was a total of 37 cases, 25 Kikuyu, 8 Jaluo, and 4 Wakamba. The controls consisted of people attending the blood bank centre for routine blood grouping, only the three tribes concerned being included. There were 2,241 Kikuyu, 813 Jaluo, and 771 Wakamba.

The table shows the numbers and percentages of the various blood groups in the control population and in the ulcer group. Among the patients with peptic ulcers there is a higher proportion with blood Group O than there is in the general population. This difference in the proportion of O blood group against other blood groups is statistically significant.—We are, etc.,

G. S. MANGAT.
J. R. HARRIES.

King George VI Hospital,
Nairobi, Kenya.

REFERENCE

[1] Aird, I., Bentall, H. H., Mehigan, J. A., and Fraser Roberts, J. A., *Brit. med. J.*, 1954, **2**, 315.

Out-dated Training of Nurses

SIR,—I had occasion recently to open a modern (1960) textbook of nursing emanating from an ancient hospital of monkish origin and famous in the training of nurses. In chapter II I found eleven enemata listed, including gruel, glycerin, turpentine, ox-bile, milk and molasses, quassia, and starch and opium, though soap was given pride of place and said to be "still the most common," and "replacing to a large extent those given below."

It is true that the syllabus for the final examination of the Certificate of General Nursing does demand the preparation and administration of enemas of various types, but should so much of mediaeval practice be perpetuated in 1960?

I looked again, and found half a page on tapping of fluid in the legs and the same on acupuncture. Now it could be that a nurse will see such methods practised once in her lifetime in Europe or perhaps a little more frequently in Nepal or Patagonia (and I do not include these places irrelevantly). Yet, surely, if there are complaints of an overcrowded curriculum some of these measures could be excluded now? Similar examples from this volume could be repeated many times over—Potain's aspirator is illustrated and described as if for use, Woulfe's bottle is described to moisten the oxygen which the patient or nurse in training will almost certainly need after seeing the aspirator, and a syringe is illustrated for aspiration of the chest which should not be used for that purpose. I am not making a criticism of the book; there are many chapters in it that are quite admirable. And it is in good company. A British medical and nursing dictionary and encyclopaedia of equally hallowed origin (1958) says, "Carminatives given per rectum for the relief of distension of the gut by flatus, are Alum, Turpentine and Asafoetida. A turpentine stupe applied to the anterior abdominal wall will also act as a carminative." I will wager that the author had neither administered nor seen administered the recommended carminatives this past 20 years.

What is of concern is the out-of-date practice of medicine and surgery which is being remembered by examining bodies, and which, therefore, presumably must be taught. Is this really the science of nursing and medicine we would wish to offer overseas candidates? Would it be too bold to surmise that the fault lies in separation of the doctors from the responsibility for the training of the nurses? Of course they give lectures and demonstrations, but it would seem that they are too little responsible for the standards and details taught when their back is turned. Even without altering that responsibility, is it not time the medical profession showed renewed interest in the education of their colleagues? Should they not issue a manual of nursing instruction?

I well realize that this criticism affects only part of the nurse's education—Florence Nightingale's "Notes on Nursing" still cover much that is needed.—I am, etc.,

C. GRIMSHAW.

The Churchill Hospital,
Headington, Oxford.

Menstrual Red Eye

SIR,—Mr. M. D. O'Brien's interesting letter (February 4, p. 359) draws attention to yet another circumstance in which menstruation appears to affect a disorder involving mucous membrane. In his patient, redness of the left eye occurred repeatedly in association with menstruation and disappeared again within two days. Whether the corneal ulcers that he detected were due to a chronic virus infection or to another cause, the symptoms disappeared in a striking way as the menstrual cycle progressed.

It is well known that aphthous ulcers of the mouth and vagina may also become worse premenstrually, and these are not the only disorders of mucous membranes to vary with the menstrual cycle: premenstrual bleeding from mucous membranes may occur in hereditary telangiectasia, premenstrual nose-bleeds are not uncommon, and oestrogens have been used in the treatment of both these conditions.[1 2]

Vaginal cytology has long been used to assess tissue-response to the sex hormones, and oestrogen is known to increase the proliferation and cornification of the vaginal epithelium. Bishop[3] has had very good results with oestrogens in the treatment of buccal and vaginal

ulcerations; in those cases which responded we (M. M. and F. O.-C.) found the ulcers occurred when the cornification index was absent or low. Cytological changes have also been observed in the urethra during the menstrual cycle and to some extent in the buccal mucosa, though the latter is less reliable.[4] In some patients receiving oestrogens we have found it impossible to diagnose nuclear sex from a buccal smear owing to the cornification of the nuclei and absence of cells from the basal layer.

Mr. O'Brien's observations have prompted us to begin further studies of the nasal and buccal mucosa and of the conjunctiva as a further test of our belief that oestrogens can stimulate epithelial cell proliferation at many different sites. If this is true, it may explain the protective effect which these hormones appear to have in a number of unrelated ulcerating or bleeding conditions affecting mucous membranes.—We are, etc.,

Guy's Hospital, London S.E.1. MAURICE LESSOF.
MOIRA MURRAY.
Chelsea Hospital for Women, London S.W.3. FREDA OSMOND-CLARKE.

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[2] Jacobson, P., *Arch. Otolaryng.*, 1954, **59**, 523.
[3] Bishop, P. M. F., personal communication, 1960.
[4] Pundel, J. P., *Les Frottis Vaginaux et Cervicaux*, 1950. Masson, Paris.

SIR,—The letter from Mr. M. D. O'Brien (February 4, p. 359) is interesting indeed, but the condition described, although perhaps not a common one, is not unknown. Duke-Elder has something to say about it in his *Textbook of Ophthalmology*,[1] and it appears to have been noted as far back as the year 1521.

At this moment I have a case attending the Croydon Eye Unit—a young married woman, of age 25, who has been coming to us for some months past with retinal oedema of the left eye, particularly affecting the macular area. All investigations directed towards the finding of a possible "toxic" source produced negative results, and she was treated with oral prednisolone. Quite recently the patient volunteered the information that her vision, in the affected eye, seemed to get worse from the first day of menstruation, deteriorating for the next fourteen days, and then gradually improving till the onset of the following period. Her visual acuity had in fact been 6/6 (with correction) on her previous visit, which was during the last week of the cycle.

I have discussed the case with a consultant colleague and with a consultant gynaecologist, and, on the suggestion of the latter that perhaps the oedema could be considered as related to the "premenstrual syndrome," with water retention, I have prescribed an oral diuretic to be taken just prior to the onset of the next period, to be discontinued at onset; we are awaiting the next visit of the patient with interest. Although the case in question is not presenting the same signs and symptoms as that of Mr. O'Brien, it does lead me to wonder if there is some common underlying factor in the pathology. We would be glad to hear of any similar case-histories and thoughts on the subject.—I am, etc.,

The Eye Unit, Croydon. A. M. ROY.

REFERENCE

[1] Duke-Elder, W. S., *Textbook of Ophthalmology*, 1938, vol. 2, p. 1507. Kimpton, London.

SIR,—I was interested to read about "Menstrual Red Eye" (February 4, p. 359). A patient, 43 years old, used to have right conjunctival hyperaemia together with "heat spots" on the forehead and below the right costal margin two days before the start of her cycle. These manifestations would clear a day or two after the period. This was her own observation over the last 28 years. Ophthalmological examination showed no abnormality except the hyperaemia. My colleagues could not give a satisfactory explanation to this condition.—I am, etc.,

Edinburgh. M. F. GIBRIL.

Medicine in North America

SIR,—One of your native poets has remarked on the advantages of seeing ourselves as others see us. Many Canadian doctors were therefore interested to read Dr. H. J. Cronhelm's appraisal of general practice in Canada (January 21, p. 194) and your leading article (February 4, p. 344). In both communications the state of general practice in this country has been appraised in very kindly terms, and we are gratified that it was possible to find so many favourable features to record.

We are proud of the work of our well-informed general practitioners and we are aware of the service which they render as members of the medical staffs of Canadian hospitals. Their participation in the activities of the large metropolitan hospitals presents difficulties which we are striving to overcome, and the Canadian Medical Association is on record as advocating a department of general practice in all Canadian hospitals large enough to be departmentalized.

Dr. Cronhelm was a welcome visitor to this country and we are grateful to him for his view of the stature of general practice in the Canadian context.—I am, etc.,

A. D. KELLY,
General Secretary,
Toronto 5, Canada. Canadian Medical Association.

Evaluation of Special Investigations

SIR,—Dr. J. W. Paulley in his letter (January 28, p. 289) advocates more training for potential general practitioners in the use and evaluation of ancillary methods of investigation. his message needs to be heard; indeed, it needs to be bellowed into the ears of those in authority who are able to take some action in the matter.

At present formal postgraduate instruction is practically non-existent in the great majority of hospitals. The old apprenticeship system still reigns supreme; the houseman learns what his chief, or the registrar, has the time or the inclination to teach him. Such a system worked well enough when medicine was a bedside art alone, but it is sadly inadequate for instruction in the use and interpretation of laboratory investigations, *x*-rays, and E.C.G.s.

In this particular respect American postgraduate education can teach us much we need to learn. The postgraduate doctor holding a hospital appointment in that country would feel aggrieved if organized tuition in pathology, radiography, and electrocardiography did not form a regular part of his daily routine. In this country the houseman is still thought of as a "convenience" for his chief. In busy provincial hospitals with a chronic shortage of junior hospital staff time for organized tuition just does not exist, yet this is the training-ground for most of our general practitioners. The solution to the problem will demand a radical

reorganization of the present system of staffing our hospitals.

Dr. Paulley also intimates with a nice delicacy of touch that the problem of interpretation of special investigations is not confined to general practitioners, but exists for the senior hospital staff as well. In this respect I am reminded of a good tale about an eminent consulting physician at a clinicopathological conference at Bart's. As he stood there he was asked to interpret the E.C.G. tracing. A bright young expert noticed that he was holding it upside down. Unable to miss such a chance, the expert tapped the great man on the shoulder, informing both him and his audience of his mistake. "In a difficult case like this," came the acid reply, "you must look at it from all angles!"—I am, etc.,

Aldeburgh, Suffolk. IAN TAIT.

Release of Bacteria from Surgeons' Hands

SIR,—Concern about the increased rates of cross-infection in hospitals led us to investigate the effect of using soaps containing germicides for surgical scrub-up. The work was done at the theatre of the Bedford South Wing Hospital.

Soap without germicide was used for the surgical scrub-up at the hospital. The hands were soaped, lathered, and rinsed as often as desired by the individual for at least five minutes; in addition hands and nails were scrubbed with a brush which was kept in 1:10,000 mercuric iodide. After the final rinse, hands and arms were swabbed with 70% alcohol and dried on a sterile towel. Samples for bacteriological examination were obtained from the operating team after operations by: (*a*) taking streaks of the middle three fingers on the right hands across a 5% serum-agar plate, (*b*) counting the number of viable bacteria on the insides of the gloves. This was done by suspending the reversed gloves by the cuffs in 2 lb. (0.9 kg.) Kilner jars containing 100 ml. of water containing 5% serum. After thorough agitation the gloves were removed and the rinsings used to make plate counts.

The mean of 10 separate examinations gave bacterial counts of 300 (range 100 to 2,200) from the inside of the glove. The mean number of organisms per finger streak was 0.6 (range 0 to 2).

Smylie, Webster, and Bruce[1] used the finger-streak technique and showed that numerous bacteria were removed from hands, and the reason for such low counts being obtained in our experiments was sought. It was interesting to note that the hands of the subjects of Smylie *et al.*[2] were wet with perspiration after operating, whilst at all times our subjects' hands were quite dry. It is generally agreed that alcohol efficiently sterilizes the superficial layers of skin, but these soon become contaminated by deeper-seated bacteria brought out with sweat. It seemed, therefore, that lack of sweat may have been the cause for so few bacteria having been recovered, and the effect of sweating was investigated. Various methods of causing subjects' hands to sweat inside rubber gloves were tried, but none were effective. Finally to simulate sweat we used 1:100 peptone water added to gloves.

The surgical scrub was standardized to three successive washes as follows: soap 15 seconds, lather 60 seconds, rinse 15 seconds. After the final rinse, hands were swabbed with 70% alcohol, dried, and inserted into sterile rubber-gloves; 0.5 ml. of 1:100 peptone water was then pipetted into each finger of one hand. Gloves were worn for 30 minutes and then they were removed and samples taken as before.

The wet hands of 18 subjects had a mean count inside the glove of 180,000 (range 1,300 to 2,000,000), but the corresponding dry hands only had a mean count of 307 (range 100 to 1,400). The finger-streaks gave similar results: the mean number of organisms per streak was 96 with wet hands; dry hands often gave streaks which appeared sterile. The mean number of organisms on such streaks was 1.2.

These results show that when the value of various scrub-up techniques is being assessed it is essential to keep the moisture-content constant inside the gloves. Also, if hands can be kept dry, the chance of infecting a wound should be reduced even if glove puncture does occur.—I am, etc.,

Food Research Department, Unilever Limited, Sharnbrook, Bedford. L. W. STUTTARD.

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Woulfe's Bottle

SIR,—Dr. C. G. H. Newman has described (January 28, p. 283) a simple Woulfe's bottle and safety valve unit for use in neonatal resuscitation. I am sure that the apparatus has been found to be effective in preventing the application of oxygen at too high a pressure to infants, but its acceptance perpetuates a concept that the Woulfe's bottle is an effective humidifier, a fact which is still reflected by the use of the bottle in a somewhat simpler form as part of standard ward oxygen-equipment.

By using a Woulfe's bottle, however, it is only possible at room temperature to raise the relative humidity of oxygen to about 75%, and when the partially humidified oxygen is raised to body temperature in the lungs the relative humidity falls to approximately 48%. As the relative humidity of alveolar air is 100%, it is clear that the inspired oxygen must have asborbed moisture from the bronchopulmonary tree, a potentially serious situation in a newborn baby or in an adult with thick sticky secretions. The situation is little better if the inspired oxygen has 100% humidity, as at body temperature this falls to 70%. Only an aerosol will overcome this difficulty. The only useful purpose served by a Woulfe's bottle is that it acts as a crude flow-meter.—I am, etc.,

Liverpool 1. EWAN F. B. CADMAN.

Splenectomy in Myelofibrosis

SIR,—We read the paper by Drs. G. Wetherley-Mein and N. F. Jones and Mr. J. M. Pullan on the effect of splenectomy in myelofibrosis with great interest (January 14, p. 84). It seems to be inescapable that splenectomy can be beneficial in this disease. This has usually been attributed to reduction of the haemolysis which so frequently accompanies myelofibrosis; if a different explanation is to be accepted the evidence in its favour must be strong. It is with this in mind that we would respectfully draw your attention to two deficiencies in the evidence presented.

The assumption that the seven-day Fe-59 utilization figure represents a reliable index of red-cell production is surprising in view of earlier reports from the same laboratory,[1 2] as well as other publications,[3 4] which have stated that the presence of random red-cell destruction invalidates this assumption. Each of the two patients reported in this paper had a shortened mean

red-cell life before splenectomy, and in Case 2 restoration towards normal was noted after the operation. Splenectomy would be expected to reduce or abolish random red-cell destruction and therefore to increase the utilization figure even if it does not affect erythropoiesis.

The evidence from surface-counting patterns is also weaker than it appears. The counting rates are expressed in absolute terms although a scale is not provided, and the most striking feature of the two tests on Case 1 is that the absolute counting rates at all sites at zero time appear to be much lower in the first test. In particular, the initial sacral activity is lower in the first test than in the second, so that the subsequent rise is proportionately greater. If the x axis position represents zero counts on the y axis the proportionate rise is approximately the same in each test. Our experience of the errors inherent in surface-counting would lead us to regard the difference between the two patterns in the second case as insignificant.

In conclusion, we would like to emphasize that we do not deny that the spleen may inhibit erythropoiesis in this disease: we merely wish to sound a note of caution against acceptance of the possibility without critical examination of the evidence.—We are, etc.,

Westminster Hospital, London S.W.1. D. E. PEGG. W. J. HARRISON.

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2 —— —— *Recent Advances in Clinical Pathology*, 1960, 3rd series, p. 247, edited by S. C. Dyke. Churchill, London.
3 Finch, C. A., Gibson, J. G. II, Peacock, W. C., and Fluharty, R. G., *Blood*, 1949, **4**, 905.
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Clinic Doctors

SIR,—There are good and bad clinic doctors just as there are good and bad doctors in any other branch of the profession. The good that clinic doctors have done in the past, especially in the prophylactic field, cannot be denied, and as long as there are clinics there will be the need for clinic doctors to staff them. However, since 1948 and the removal of any financial bar to seeing the G.P., is there any need for the continuance of the local health authority clinics? At present many patients attend both and consequently often receive conflicting advice. In answer to Dr. F. Groarke (February 4, p. 362), I think that most G.P.s will be familiar with the following: (1) The anxious mother who has been sent by the clinic doctor to get a "good tonic" for her healthy child; (2) the child sent by the clinic or school doctor to get the ears syringed when the small amount of wax present is not causing any symptoms; (3) the mother requesting a hospital letter to have baby circumcised on the advice of the clinic doctor when there is no medical reason for this; (4) the night call to the vomiting infant who is being fed on advice by the clinic doctor which is contrary to your own beliefs; (5) the anxiety caused in parents by the clinic's emphasis on averages (e.g., weight and height) and routine procedures.

I think that the majority of family doctors prefer to be solely responsible and in charge of their patients unless they have occasion to refer them for specialist or hospital treatment. I cannot see that it is necessary to share the care of the childhood of the patient with someone who is not aware of the family set-up as a whole, and whose opinions may differ from the family doctor who is ultimately responsible. This is in no way a reflection on the clinic doctor's competence, but I, for one, find their presence superfluous.—I am, etc.,

London S.E.23. C. R. LYNN.

SIR,—The point about the clinic doctors is not that they are not nice chaps but that they are redundant—(in the polite modern euphemism) totally, completely expendable. Let us grant, with our tongue in our cheeks, the superb job they have done in the past. At least, a case can be made out, but surely, *now*, there is not one single activity of the clinics which is not a total waste of public money.

Are G.P.s not capable of immunization, and why are the clinic doctors still doing antenatal work? They are bound to be bad at it because they do not attend confinements. And their clinical work—how can they possibly be good clinicians when they never deal with really sick children? Health visits, preventive medicine—twaddle! Anyone who thinks that the young mother of to-day needs a health visitor is living in the past. And what of special clinics, dental, orthopaedic, ophthalmic, etc.? Is there any need to maintain these as separate entities? Even the school inspection system is a total extravagance. Each child in the first 15 years of its life must be seen at least 40 times by its G.P. Why cannot G.P.s do the school inspections in their own surgeries? The idea that the modern parent is careless of his child's health is also quite out of date.

It appears that the State is financing an expensive, unnecessary, inefficient, duplicate service for no reason at all. Even if this service were up to date and efficient, which it is not, it would be a ludicrous extravagance. If the G.P.s are not fit to do the work of the clinics, in their own surgeries, they are not fit to be at large. The Minister of Health should consider abolishing the lot. I personally would welcome it if only to ensure that never again would a parent say to me, "The clinic said he was anaemic and gave him some Parrish's food."—I am, etc.,

London N.W.4. R. W. COCKSHUT.

SIR,—May I add a few final words to the correspondence on clinic doctors? As assistant M.O.H. and school medical officer my work includes school medicals, baby clinics, immunization sessions, assessing children for special schools, examining council employees, and giving dental gases. Much of this work is necessary and really appreciated by the mothers and overworked G.P.s here. Many problem families are sorted out between clinic doctors, school teachers, child welfare officers, and G.P.s. Naturally some of the work is a little boring and appears unnecessary at times, but is not that so in all branches of medicine?

There are always a few G.P.s who seem almost obsessional about their status as family doctors and appear to regard the patients on their lists as personal property not to be tampered with by anyone, let alone the poor assistant M.O.H. They are very sensitive beings, and letters abound not only to the public health departments but to the local hospitals, district nurses, and the *B.M.J.* Happily, relationships between clinic doctors and most G.P.s here are very satisfactory, the welfare of the patient, after all, being our main consideration.—I am, etc.,

Ipswich JEAN GILLBARD.

Prevention of Dental Caries

SIR,—Your interesting leading article (January 28, p. 262), as a summary of what is regarded as the present views upon the prevention of dental caries, is surely too limited in its scope. Although the work of Miller is recognized, no other reference to the attacking organisms is considered. The cause of the pathological lesions is of the greatest importance whatever defences there are. If a comparison be made with pulmonary tuberculosis, the nature of the bacillus and its activities were of far greater importance than the defensive factors, whether structural or biochemical, and what a wonderful change has been effected. Surely this also applies to dental caries. The bacteriologist is most likely to help us, but he seems to have been relegated to a less important role at the moment—a very long interval considering the importance of the direct cause.

On re-reading the papers upon the work he did during the early years of 1920[1] in the Bland Institute of Pathology at the Middlesex Hospital, the conclusions reached were of sufficient importance for reference at least to be made. With the great advance in methods continuation of this work seems to be worth while. Our conclusions may be of sufficient interest to repeat: (1) The examination of selected carious material showed the constant presence of a definite type of bacillus. (2) The bacilli are capable of producing a high degree of acidity by the fermentation of carbohydrates. The average final *p*H value of nine strains was 2.75, which is sufficient to decalcify teeth. (3) Teeth left in contact with pure cultures over prolonged periods showed changes almost identical with those found in natural caries. (4) Such teeth show erosion of the enamel with penetration of the dentinal tubules and the formation of liquefaction foci. (5) The bacilli, to which we propose to give the name *B. acidophilus odontolyticus*, in their resistance to and formation of acid resemble the "acidophilus" group of Moro; biologically, however, there are several points of difference.—I am, etc.,

London W.1. W. WARWICK JAMES.

REFERENCE

[1] McIntosh, J., James, W. W., and Lazarus-Barlow, P., *Brit. J. exp. Path.*, 1922, **3**, 138.

More Market Research

SIR,—I have to-day received a letter from an organization called Intercontinental Medical Statistics Ltd. asking me to take part in a survey amongst general practitioners. The number of the book of forms sent with the letter is 5945, so it seems that a large number of practitioners have been circularized and it is probable that some are going to help in collecting data for I.M.S. Ltd.

Information is required about the age of patients, their sex, the diagnosis, drugs used, total quantity and presentation, but not dose prescribed, the "desired therapeutic effect," place of consultation, and hospital referral if relevant. Also the type and size of practice, and whether dispensing is undertaken. This information is to be recorded about every patient seen on two successive days; in fact the two days following the arrival of the request.

As an incentive to do this the firm offers a gramophone record of heart-sounds to participating doctors.

Intercontinental Medical Statistics Ltd. is described by Mrs. Montague Brooks, whose facsimile signature is at the foot of the letter, as a "medical research firm." I am interested to find that they share a telephone number with an organization called International Marketing Services Ltd. The letter goes on to state that the firm is trying to discover more about methods of treatment in current use, and they hope the information gathered will be helpful in developing and improving methods of treatment. This information will, they say, be used by industry and medical investigators.

I am unable to find any reference to I.M.S. Ltd. in any of the medical reference books at my disposal, but I have no reason to suppose that the company is not actuated by the highest ethical motives in its desire to collect information from general practitioners. I gather that I.M.S. Ltd. is advised by statisticians of high repute. I wonder what weight is going to be given to the lack of figures from those practitioners like myself who were selected but who are not prepared to participate in this survey.

I for one am unwilling to allow my practice to be used for so-called "research" unless I know for what purpose and by whom the figures so obtained will be used. I would also require an undertaking that the analyses of these figures would, if possible, be published and that they should in no circumstances be sold as information on which to base advertising or any aspect of marketing. I hope and suspect that most of my colleagues in general practice will feel the same.—I am, etc.,

Knebworth, Herts. RICHARD GARDNER.

Insulin-independent Young Diabetics in Natal

SIR,—It was a privilege to have Dr. J. E. Cosnett (October 15, p. 1150) comment so fully on my recent observations about insulin-independence in young Natal Indian diabetics (August 13, p. 537), and I would be grateful for space to reply to his remarks.

In reporting his experiences with oral therapy in 55 Natal Indian diabetics he says: "Using urine tests and random blood-sugar estimations as criteria of control, we have found that the oral therapy has substantially affected the diabetic state in less than one-fifth of the patients." I would be the first to admit that the 1,200 patients that we have on oral therapy in the King Edward Hospital Diabetic Clinic in Durban are not as fully documented as Dr. Cosnett's 55 patients in Maritzburg, with the possible exception of 300 of them, in whom careful studies on total fats, fibrinolysins, serum mucoproteins and cholesterols have been combined with random blood-sugars. But we are glad that Dr. Cosnett has been able to confirm in his series what we had found in our 300 patients—namely that, on the basis of random blood sugars and urines, diabetic control does not seem to be satisfactory in the Natal Indian on oral therapy. We had not troubled to note this fact, because of the observations of many workers on the drug mentioned by Dr. Cosnett, chlorpropamide—epitomized by the studies of Jackson and Herman[1] in Capetown, who showed that the effect of the drug even in patients who responded satisfactorily was on the "*basal or fasting blood level rather than on the disposal of ingested carbohydrates.*" We are surprised therefore to read that there are still doctors who use random blood-sugars and urines in their attempts to assess the efficacy of a drug which when successful in diabetes *affects the fasting sugar level alone.* In spite of the fact that we have never used routine random blood-sugars in assessing response, we noted[2] early on in our trials that marked subjective improvement occurred even when blood-sugar levels were apparently not returned to normal levels, and even if there was not a significant decrease in urine-sugars.

I feel that Dr. Cosnett has perhaps missed the main point of my letter, which was to show that there are very different therapeutic implications in the under-40 Natal Indian diabetics between those that are fat and those that are thin. Far from my observations echoing his "findings largely," they show that very large numbers of these young diabetics are independent of exogenous insulin—exactly as a group of pre-diabetics would be—*in the normal course of events*. They only appear to require insulin to tide them over caesarean section or induction. Therefore we propose to continue calling such patients "insulin-independent young diabetics," as the term is accurate and descriptive—a good response to the oral drugs being a *sine qua non* of the diagnosis.

In our present series of cases we find it a good rule to regard as "J" types all *thin* young Natal Indian diabetics who require over 100 units of insulin for better health, and those *thin* young patients who respond to the oral drugs. We have been able to wean half of Dr. Cosnett's "J" types (who have not subsequently become ketotic insulin-dependent patients) on to oral therapy. So many of Hugh-Jones's original "J" types[3] have developed into ketotic diabetics that Tulloch (personal communication) doubts the existence of the syndrome. Strangely enough, truly insulin-dependent and ketotic Natal Indian diabetics seldom require more than 40 units of insulin daily.—I am, etc.,

The Diabetic Clinic,
The King Edward Hospital,
Durban, Natal.

G. D. CAMPBELL.

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3 Hugh-Jones, P., *Lancet*, 1955, **2**, 891.

Fathers at Delivery

SIR,—The normal father would run a mile if asked to witness his wife's delivery. The normal mother would "see him further," to use the local idiom. With the notorious exception of the male seahorse, who incubates, and then gives birth to his young in an alarming explosion (serves him right), the sires of the animal kingdom, including *Homo sapiens*, tend to keep well out of the way when parturition is in progress.

Let us not pander to morbid curiosity and sensationalism, nor to those featherbrains who wish to be in the van of a new fashion, by encouraging a highly unnatural trend with the mumbo-jumbo of pseudo-psychology. The proper place for the father, if not at work, is the "local," whither instinct will usually guide him. Family men may be baby-sitting, unless ejected by mother-in-law.—I am, etc.,

Tyrone County Hospital,
Omagh, Co. Tyrone,
Northern Ireland.

J. H. PATTERSON.

SIR,—I would like heartily to endorse Mr. D. W. Hill's view (February 11, p. 430) on this subject. To me the father seems the only person to assist his wife at this time in a way in which no midwife is able to do. By assist I mean actually helping his wife to bear down, holding the legs at contractions, giving encouragement, reporting on progress, and then, when eventually the baby is born, being the first to say whether it is a boy or girl.

The husband is there at the marriage and he should be there at the birth of his children. Why is the husband a typical caricature of a man at the time of delivery? Because he knows in his heart of hearts he should be assisting his wife in a joint effort. Why does he appear sheepishly with a bunch of flowers when it is all over? Because he feels terrific guilt at being absent in a crisis concerning them both. Why is he made to feel ostracized by being made to first see his baby through glass or with a mask on? Because the chances are that the baby is already immune to his bacterial flora anyway.

Many educated and mature husbands I talk to would like to be present, but cannot override conventions. We must assist them. G.P.s must encourage fathers to make arrangements for their wives to have children at home and take time off to be present at the delivery. Father is often also the best domestic help. Fathers should be encouraged to attend antenatal classes and health education groups to understand what is involved in normal labour and what part they have to play. Emotionally they have to mature sufficiently in the same way as their wives. In short, fatherhood as an ideal has to be reinstated and put back on its pedestal. The pathetic chain-smoking, restless, and flower-offering expectant father should be a figure of the past. The paternal instinct is as strong as the maternal and should not be frustrated. Even the male stickleback hatches the young and many male birds take a turn on the nest.

But at present a man marries a woman for better or for worse, for richer, for poorer, through sickness and in health till death (and presumably the obstetrician or midwife) do them part.—I am, etc.,

Amersham, Bucks. BRIAN H. BURNE.

SIR,—Mr. D. W. Hill's letter (February 11, p. 430) calls welcome attention to a problem which has been exercising obstetricians for some time—should we allow a husband to witness the birth of his baby? Mr. Hill himself believes that he should be welcomed and encouraged to do so, that his presence on this occasion is conducive to subsequent marital and family happiness, and that this may be gravely impaired by his exclusion.

But is this really true? Shorn of its ideological aura, the actual process of birth is a pretty unglamorous affair. The periodic distension of the vulva, the accompanying discharge of faeces and urine, and the public exposure of parts usually described as private do not make an edifying spectacle, and one sometimes wonders how a husband who has watched all this can ever have intercourse with his wife again. And, apart from the aesthetic shock, the witnessing of an episiotomy, a perineal laceration, a brisk haemorrhage or the resuscitation of an asphyxiated baby may have dire physical results in a layman sitting masked and gowned in the atmosphere of the delivery rooms. Indeed, I recently had to utilize the perineal sutures prepared for a mother for the repair of an extensive scalp laceration in her husband, who had fainted and fallen at the sight of the "happy" event.

Most obstetricians and midwives feel hampered and embarrassed by the presence of the father at delivery. They regard it as sadistic and unnatural curiosity, and are constantly afraid that his reaction to a possible abrupt complication may hinder their work. The mother herself, while often wishing to have her husband with her during the first stage, usually wishes to spare both herself and him the physical embarrassment of the second, for most young women are still essentially modest and considerate. It is true, as Mr. Hill says, that

the birth of a child is the creative climax of the physical relationship between husband and wife, but it would be a pity to spoil it by disillusionment.—I am, etc.,

London W.1. ALBERT DAVIS.

Infectious Mononucleosis

SIR,—Your correspondents, Dr. D. P. Mullan and Dr. I. M. Librach (January 28, p. 289) and Dr. B. L. P. Dalton and Dr. A. N. M. Davidson (February 11, p. 425), are only half correct in their observations on palatal petechiae in infectious mononucleosis. It is true that oral petechiae occur in a number of other diseases, notably virus infections and, of course, blood dyscrasias (I recently noted them inside the cheeks in a boy with mumps before the parotid glands enlarged), but in the common virus infections they are transient and last no more than a day or two.

In infectious mononucleosis they are often remarkable for their size and number, being at first most obvious on the soft palate, but frequently extending well forward over the whole hard palate. They are distinguished, too, by their persistence over many days or even weeks, apparently recurring in fresh waves every three or four days. I had one patient whose palate was still covered with petechiae four weeks after their first appearance when the diagnosis of infectious mononucleosis had been confirmed by blood investigations.—I am, etc.,

Bletchley, Bucks. B. L. E. C. REEDY.

Medicine Broadcast

SIR,—"Emergency Ward 10" has achieved some superficial respectability by attention to technical details. Now it appears to have won full honours by being praised by the B.M.A.'s memorandum to the Pilkington commission on broadcasting; and, indeed, by inclusion under the heading of "Medicine Broadcast" in your annotation (February 4, p. 348); "Illness Dramatized" would be a more fitting description. It appears to be produced to appeal to the same emotions which lead old ladies to swop gory stories about their operations. Recently, the management of an expectant mother with chronic rheumatic carditis was cloaked with mystery, doubtless necessary for dramatic effect, but terrifying for a real-life character so placed.

Richard Gordon's boisterous, if somewhat Rabelaisian, humour makes more appeal to the healthy-minded than the insipid pseudo-cultural young men of "Emergency Ward 10."—I am, etc.,

Barton-on-Humber, Lincs. S. H. F. HOWARD.

Complimentary Photography

SIR,—Recently a photograph of myself was published in a prominent place in a London newspaper without my permission. I found that it had been supplied by a well-known photographer to whom I had given a complimentary sitting. I was under the common impression that, if I ordered and paid for copies of the photograph, the copyright would pass to me. I find that this is not the case.

Members of the profession should be warned that they should either refuse complimentary sittings or grant them only on a written undertaking that copies will not be supplied to the lay press.—I am, etc.,

London W.1. RAYMOND GREENE.

Obituary

H. R. DEAN, M.D., LL.D., D.Sc., F.R.C.P.

Professor H. R. Dean, professor of pathology in the University of Cambridge since 1922 and formerly Master of Trinity Hall, died at Derby on February 13. He was 82 years of age.

Henry Roy Dean was born on February 12, 1879. From Sherborne he went on to New College, Oxford, where he took first-class honours in the School of Natural Science. He completed his medical training at St. Thomas's Hospital, graduating B.M., B.Ch. in 1904. He took the M.R.C.P. in 1906, proceeded D.M. in 1912, and was elected F.R.C.P. in 1913. After graduation he obtained a senior demyship at Magdalen College, Oxford. At St. Thomas's he was medical registrar in 1906 and resident assistant physician in 1907. In 1909 he gained the Radcliffe Travelling Fellowship of the University of Oxford, and went to study in Berlin in Wassermann's laboratory. On his return to England in 1910 he was appointed assistant bacteriologist at the Lister Institute. He then became professor of pathology and bacteriology in the University of Sheffield (1912–15), and professor of pathology in the University of Manchester (1915-22). He was elected to the chair of pathology at Cambridge in August, 1922. In 1925 when new statutes were introduced he chose to continue under the old statutes, and he lived to become the last holder of a post in the university with no age limit for retirement—a matter for quiet satisfaction. As professor of pathology for 39 years he served under six Regius professors of physic, and, when Professor Ryle suddenly left Cambridge at the beginning of the second world war, Dean was appointed deputy professor of physic, the duties of which he carried out until the election of Sir Lionel Whitby in 1945.

[Walter Stoneman

Professor Dean was at Manchester during the first world war. He was a major in the Territorial R.A.M.C., and organized a scratch team of biologists and others whom he trained to do the bacteriological and immunological work of the 2nd Western General Hospital. He also reorganized the teaching of pathology in the University of Manchester and was for a time dean of the medical school. It was here that his views on medical education and the teaching of pathology began to crystallize, and when the Edinburgh Pathological Club conducted an inquiry on "The Training of the Student of Medicine" he welcomed the opportunity which they gave him to make his views known to a wide public.

When Dean came to Cambridge in 1922 he sought means to put his opinions on the teaching of pathology into practice. The department of pathology was a small one, inadequately housed in the medical school in Downing Street, and the only teaching was for the 2nd M.B., Part 3 ("bugs and drugs"), and some postgraduate teaching for the Diploma of Public Health conducted by Dr. Graham-Smith. Pathology had no place in the natural sciences tripos. Dean insisted that pathology should be taught in the N.S.T., and by Grace of June 13, 1924, it was included as a subject for Part II of the natural sciences tripos and the first course was commenced that year. This has proved to be a landmark in the history of pathology. For many years Dean undertook much of the teaching himself. His lectures and

practical classes on immunology provided a course which was unique in this country. He also gave an admirable course of lectures on the biology and histology of tumours. His teaching was always firmly based on his own personal experience. Over 500 students have taken the Part II course since its creation: many of them now occupy professorial or other important positions, not only in pathology but in other branches of medicine. They are a living memorial to the vision, energy, and enthusiasm of Dean. When a presentation was made to him on his 70th birthday the response from Part II students was overwhelming; letters came from all parts of the world containing expressions of affection and gratitude.

During his early years in Cambridge he was also engaged in finding money and making plans for the building of a new pathological department in Tennis Court Road. This was occupied in September, 1928. It should be noted that he was not only promoting human pathology but was pressing the claims of animal pathology, for which a suite of rooms was reserved on the ground floor of the new department. He worked constantly for the establishment of a school of veterinary science in Cambridge.

Dean was one of the most active members of a syndicate appointed in 1931 to consider the medical courses and examinations. Its recommendations, approved by Grace of May 26, 1934, gave rise to great changes in the medical curriculum within the university; except for minor changes they are still in force. The 2nd M.B., Part 3, was discontinued, and pathology was introduced as a half-subject in Part I of the natural sciences tripos. Entirely new courses in pathology were started in 1935. These were for preclinical students, and there was much discussion and many doubts, especially outside Cambridge, on whether pathology could be taught to benefit them. There is no doubt now. The course has been a success. Dean gave a carefully planned course of 58 lectures to which practical work was integrated. He always tried to put in an appearance at the practical classes. Enveloped in a linen gown, carrying his own stool, and smoking his pipe, he would move from one group of students to another; often he would have a group of students round him long after the class had officially ended. These informal talks brought him in personal contact with many students and were much appreciated by them.

Immediately after coming to Cambridge he became a Fellow of Trinity Hall, and was Master from 1929 to 1954. He was Vice-Chancellor of the University from 1937 to 1939—the anxious pre-war years. Until about this time he had produced a steady contribution of papers on various aspects of pathology, the most important being concerned with immunology. He was particularly interested in the essential unity of the serum reactions. When he ceased to do much experimental work himself he encouraged and guided others, and the publications on immunology from his department have shed light on many aspects of this subject.

During the second world war his department was reorganized to accommodate a number of visitors, including the Galton Laboratory blood-grouping unit and the M.R.C. Emergency Public Health Laboratory. Dean himself organized a voluntary blood transfusion donor service which later continued as the East Anglian blood transfusion unit. After the war there was the arduous task of reorganizing the department of pathology and the school of clinical research which it had been hoped that Professor Ryle would create. The burden of this work was on Dean as deputy Regius Professor and chairman of the Faculty Board of Medicine until Sir Lionel Whitby came as Regius Professor of Physic in 1945. The department of pathology has emerged stronger and more active than ever before and more closely bound to medicine. In 1918 Dean said to the Edinburgh Pathological Club: "To my mind pathology and medicine form one whole, and it is as difficult to think of pathology without medicine as I trust it is impossible to think of medicine without pathology." The spirit of this governed all his endeavours.

For many years Dean was secretary of the Pathological Society of Great Britain and Ireland, and was always a prominent figure at the meetings, which he rarely missed. After the war he founded the East Anglian Pathologists' Club, which has flourished since and brought closer together pathologists in that area. He was chairman of the council of the Imperial Cancer Research Fund from 1941 to 1956. Its advice on matters concerned with medical education and pathology was sought by many official and unofficial bodies, and generations of medical students and young pathologists have sought his counsel about their careers and personal affairs.

Professor Dean was elected an Honorary Fellow of New College in 1953. He was an honorary LL.D. of two universities—Aberdeen and Western Reserve—and an honorary D.Sc. of Liverpool University. At Annual Meetings of the B.M.A. he was vice-president of the Section of Microbiology in 1922 and president of the Section of Pathology and Bacteriology in 1948. He was a governor of Sherborne School, and in 1934 he served on the Royal Commission on the University of Durham.

Dean had many interests apart from medicine. He was a strong swimmer, and on summer afternoons was usually to be found at the varsity bathing place. He was an ardent follower of university rugby and attended the Oxford and Cambridge match regularly until last year. During the May and Lent races he accompanied the boats on his bicycle to his own danger and that of the public on the towing path. Last year his bicycle was confiscated. In his youth he had climbed in the Dolomites and he had a great love of Austria. In recent years he often went for long walks in the New Forest (carrying an axe with which to cut down ivy) with his old friend Dr. Garbett, the late Archbishop of York. He also walked in East Anglia with Dr. Peyton Rous.

Dean was an authority on College silver and a collector of old silver for many years. His love and knowledge of it went back to the time when he was a resident at St. Thomas's Hospital and he became friendly with Mr. Percy Webster, a Mayfair antique dealer. He was fond of good food and wine, of which he had no mean knowledge, and his dinner parties, at which he was a perfect host, will be remembered by many medical visitors to Cambridge. When he had to leave Trinity Hall Lodge and he was looking for a house he said to me, "My wants are very simple: all I want is a library for my books, a place in which to keep my silver, and a cellar for my wine." His memory will remain green in the heart of his students, his colleagues, and all who knew him well as a great teacher of pathology and an exponent of the art of gracious living.

He had a happy family life, and he could not have engaged in his numerous activities without the solicitous care of Mrs. Dean, whose death a year ago was a sad blow to him. His son, Sir Patrick Dean, K.C.M.G., and his daughter, wife of the Venerable J. F. Richardson, brought him several grandchildren who gave him great joy.—R. W.

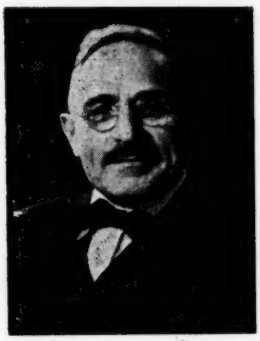
W. MAYER-GROSS, M.D., F.R.C.P.

Dr. W. Mayer-Gross, the distinguished psychiatrist, died suddenly at his home in Birmingham on February 14, aged 72. He had recently retired from the post of senior fellow in the department of experimental psychiatry of the Birmingham medical school.

Dr. E. T. O. SLATER writes: With the death of Dr. W. Mayer-Gross, European psychiatry has lost its most outstanding personality. It is due to him more than to anyone else that British psychiatry has remained within the European tradition, within which it has come to play a leading role.

Born on January 15, 1889, in Bingen-am-Rhein, Germany, Willy Mayer-Gross completed his medical education in the Universities of Heidelberg, Kiel, and Munich, and graduated M.D. at Heidelberg in 1912. He was then clinical assistant to Professor Friedrich v. Müller in Munich. During the

first world war he served as a medical officer in the German army, for the last two years in a military hospital for the treatment of nervous diseases. Thereafter for six years he was an assistant in the psychiatric clinic of the University of Heidelberg to Professors F. Nissl and K. Wilmanns, and for a further nine years, from 1924 to 1933, he was deputy director of that clinic, lecturer in psychiatry, and from 1929 associate professor of psychiatry in the university. From 1928 to 1933 he was editor-in-chief of the monthly journal *Der Nervenarzt*. These years at Heidelberg were interrupted from 1922–3, when he held a research fellowship at the Swiss mental hospital of Rheiman.



The nine years he was at Heidelberg identified Mayer-Gross with the Heidelberg school of psychiatry, then the most active in all Germany; other representatives, such as Beringer and Gruhle, were equally men of international distinction. This school attacked the task of discovering diagnostic criteria in the confused welter of psychological observations that could be made on psychiatric patients, the method employed being exact observation and precise description of often very subtle mental experiences. The approach has been called "phenomenological," and it supplied a logical complement to the work of the Kraepelinian school in sorting out forms of mental disorder by long-term follow-up. Mayer-Gross presented a full account of the work of this school on schizophrenia in the volume devoted to that disorder in the great *Handbuch* of neurology and psychiatry edited by Bumke.

In 1933 the situation of the Jews in Germany was becoming critical, and those who held academic appointments were being dismissed. Fortunately, however, Edward Mapother was able to enlist the help of the Commonwealth and Rockefeller Foundations, and to bring three of the threatened psychiatrists to the Maudsley Hospital. Mayer-Gross with his colleague Erich Guttmann constituted the department of clinical research at the Maudsley, which became a precedent and a model for similar departments at other hospitals. The influence which these outstanding men had on the teaching of psychiatry at one of the country's main teaching centres can hardly be overestimated.

Some months before the outbreak of war in 1939, Mayer-Gross accepted an appointment as consultant psychiatrist and director of clinical research at Crichton Royal Hospital, Dumfries. He passed the qualifying examinations of the Scottish Royal Colleges, and was admitted to the *Medical Register*, being naturalized a British subject the following year. At Dumfries he again built up a very active research department and had, as always, an immensely stimulating effect on the younger colleagues. When he reached retiring age in 1955, with his energy and enthusiasm unimpaired, he was unwilling to accept a life of leisure; and he came to Birmingham as senior fellow in the department of experimental psychiatry and director of clinical research at the Uffculme Clinic. His death came only a few weeks after he had at last relinquished all salaried appointments, and a few days before he planned to return with his wife to their own house in Heidelberg, temporarily sequestrated but again their own.

In recognition of his many scientific contributions Mayer-Gross received the diploma of Membership of the Royal College of Physicians of London in 1945, and was elected Fellow in 1951. He was president of the Psychiatric Section of the Royal Society of Medicine in 1954 to 1955. At the time of his death he had been nominated for an honorary degree of Doctor of Science in the University of Durham. In 1952 and again in 1956–7 he was appointed a mental health consultant of the World Health Organization, and sent on a mission to Bangalore. Here he helped to build up the first Indian psychiatric clinic with full facilities for teaching and research, and to teach the teachers.

If Mayer-Gross excelled as a teacher by word of mouth, at the bedside, or in the clinical conference, his influence was diffused to a world-wide audience through the medium of his writings. The textbook *Clinical Psychiatry*, of which he was the senior author, appeared in 1954 and has recently gone into a second edition. It has been translated into Spanish and Italian, and a German translation is on the way. The first two volumes of *Psychiatrie der Gegenwart*, the long-awaited modern supplement to the historic *Handbuch*, have now appeared, with Mayer-Gross as one of the principal editors. However, he was no less gifted as a research worker and as a fertilizer of research than as an expositor. His contributions, embodied in nearly a hundred papers, cover a very wide field.

Apart from his fundamental work on the psychology of schizophrenia, a major advance was made in the psychiatry of organic brain disorders by his studies of apraxia and the development of a methodology of psychiatric examination in cases of organic disease, embodied in the book written with R. Klein. The insulin coma treatment of schizophrenia became in his hands not only a technique of treatment but a model psychosis which could be investigated along neurological, psychiatric, and biochemical lines. Mayer-Gross was in fact a pioneer in this country of biochemical investigations in the psychoses. His clinical and methodological contributions to the experimental psychoses produced by mescaline and lysergic acid are now classical; this work, together with his well-known paper on depersonalization, shows that his scientific curiosity was stimulated by an element of the *outré*. He also pioneered the first satisfactory psychiatric demographic survey in this country. This is only a selection from the fields in which the research worker finds that among the basic papers he has to study will be one or more by Mayer-Gross.

It is not surprising that the personality of this remarkable man was in keeping with his career. Of somewhat less than average height but sturdily built, he was compact of energy and vigour, with a driving persistence and courage to face all eventualities. His spirits were always excellent, and few, if any, have seen him depressed. Good-humoured, friendly, companionable, he was able to criticize and to encourage his pupils without pomposity or condescension. Through a life disturbed much more than most by medical politics, both in his own and his adopted land, he fought his battles with vigour while remaining on good terms with everybody. The handicap of coming here as a foreigner of middle age, though it stood in the way of attaining the highest positions in Britain, never impaired his gusto and enthusiasm. This rich enjoyment of life was perhaps his most endearing feature, for, with the capacity to be at times somewhat trying, he succeeded also in being a lovable man.

The sympathy of his innumerable medical friends will go to his wife Carola, whom he married in 1919, his son, and his mother, who also survives him.

LADY JEFFERSON, M.R.C.S., L.R.C.P., D.P.M.

Lady Jefferson (née Flumerfelt), founder and medical director of the Family Welfare Service in Manchester, died in Manchester on February 10. She was 75 years of age.

Lady PLATT writes: The death of Lady Jefferson, within a fortnight of her husband, has brought to its close a rich and varied life.

Gertrude Flumerfelt was born in Canada on May 21, 1885, and was of Dutch and Yorkshire descent. She finished her formal education in Europe, where she travelled extensively and became an accomplished linguist. She was an ardent reader of the European classics and, even at this early age, became interested in the workings of the human mind. After her return to Canada she decided to study medicine, if possible in a British University. She met with

some opposition from her parents, but finally entered the Manchester medical school in 1907, qualifying M.R.C.S., L.R.C.P. in 1912. She married Geoffrey Jefferson a year later.

During the first world war her husband was posted to the British Red Cross Hospital in St. Petersburg. With characteristic resource, Gertrude Jefferson persuaded the authorities to allow her to join him and stayed until the October Revolution obliged her to return to England. After the war the family came to Manchester. The next few years were devoted to bringing up her family (she had three children) and doing part-time work in maternity and child-welfare centres. It was while working in these centres that she became impressed by the amount of mental suffering which resulted from unsolved family problems. She felt that with the right kind of help a good deal of this suffering could be avoided. She took the D.P.M. in 1937 and was appointed assistant psychiatrist to the Manchester Royal Infirmary in 1939. She also built up a successful private practice.

Her interest in family problems remained. She won the support of the medical officer of health, and a new service, the Family Welfare Service, was started in 1948. She had selected a team of workers who were prepared to work on a part-time voluntary basis. The Manchester Corporation gave her a grant and allowed her to use maternity and child-welfare premises. The service was unique in that it was a preventive service against mental ill-health sponsored by the public health department. Before her retirement Lady Jefferson had the satisfaction of knowing that the Corporation of Manchester had become convinced of the value of the Family Welfare Service to the community and had agreed to accept full responsibility for it.

Lady Jefferson was therefore a pioneer. She combined with this a love of humanity and a strong religious sense. Although of great personal integrity, she had sympathy with the frailties of human nature and was tireless in her efforts to relieve mental suffering. She has left a gap which it will be difficult to fill.

F. T. BURKITT, M.D., D.M.R.E.

Dr. F. T. Burkitt, consultant radiologist to the Kingston Hospital and other hospitals near London, and a Fellow of the British Medical Association, died on February 1, aged 69.

Frederick Thomas Burkitt was born on November 16, 1891. When the first world war broke out he had just taken first-class honours in the Natural Sciences Tripos at Cambridge, and he thereupon obtained a commission in the Queen's Royal Regiment, and it was some years before he was able to continue his medical education at St. Bartholomew's Hospital. Qualifying in 1918, he graduated M.B., B.Ch. in the following year, and took the D.M.R.E. in 1922. After qualification he held the post of house-physician at his teaching hospital and then became clinical assistant in the *x*-ray department at King's College Hospital and medical officer in charge of the *x*-ray department of the Ministry of Pensions in Chelsea. Eventually he went into practice in Wimbledon, combining this with work as a consultant radiologist at Kingston, Nelson, and Merton and Wimbledon Hospitals. During the second world war he was honorary secretary of the Kingston-on-Thames local medical war committee, and in later years he was secretary of the Surrey Local Medical Committee.

Dr. Burkitt is survived by his widow and by a son, who is a doctor, and a daughter.

J. V. O'S. writes: It is with great regret that the numerous friends of Dr. F. T. Burkitt, of Wimbledon, heard of his death. I had the pleasure and privilege of knowing him for 25 years as a colleague, as a member of the B.M.A., and as a friend. He was one of the doctors who combined hospital appointments in radiology with a small private practice, and did both excellently. He was also a staunch supporter of the B.M.A. During his life he had in turn been honorary secretary and chairman of the Kingston-on-Thames Division, and up to the day of his death he was our public relations secretary, and an excellent one he was. Last year he was made a Fellow of the B.M.A. for his outstanding services. For many years he had held the appointment of secretary to the executive committee for the Surrey area. All who have known Dr. Burkitt will mourn his death, and we extend to his widow our deep sympathy.

G. F. E. DYKE, M.B., B.S.

Mr. G. F. E. Dyke, emeritus surgeon to the Derbyshire Royal Infirmary, died in that institution on January 29, aged 74 years.

Gerald Ferdinand Eugene Dyke was educated at Brecon College and received his medical training at University College Hospital, graduating M.B., B.S in 1910. In this hospital he was casualty officer, house-surgeon, and house-physician, and then held the posts of house-physician at the Queen's Hospital for Children, Hackney, and house-surgeon to the Sunderland Royal Infirmary. He went to Derby in 1913 as house-surgeon at the Derbyshire Royal Infirmary, and soon showed his worth. During the first world war he became resident surgical officer and was given charge of the *x*-ray department. His work in the hospital during the war was so exceptional that he could not be spared for military duty: two out of four honorary surgeons were called to the Forces, wounded soldiers were admitted to special wards, and Mr. Dyke carried the major part of the surgical side of the hospital.

In 1919 he went into practice with Dr. Broster in Wirksworth, where he was very popular with the patients. But in 1921 he was appointed honorary surgeon to the Derbyshire Royal Infirmary, and he remained one of the leading consultants in the area till his retirement on reaching the age limit in 1952. He always put his hospital duties first.

For thirty years, with only a gap of two years in general practice, he was leading surgeon in the Derbyshire Royal Infirmary. As a pioneer he established the genito-urinary department and he did brilliant work in thyroid surgery. His manner was quiet and retiring, but his judgment was sound and his surgical skill complete. His house-surgeons and the ward sisters always knew his value; his anaesthetists respected him; he was an ideal colleague. His patients liked him and many doctors and their families owe him gratitude. Without taking a prominent part in committee work or medical societies, he was a regular attender, and his advice was sought, and usually acted upon, by his medical colleagues in both these important activities.

He married Miss Ethel Jane Northwood in 1925, and she and a daughter survive him.

R. P. B. writes: The many ex-house-surgeons and members of the nursing staff who worked with Mr. Dyke in the old days will regret the passing of this shy, pensive, kindly man, who nevertheless could be a merry companion in company that he liked. He had the gift of commanding great devotion from those who worked closely with him, and he maintained his high position in the profession in Derby without a trace of show. He kept his sly sense of humour to the end. When asked how he felt, he answered, "They say I feel very well"—and laughed. In spite of all the care and attention lavished on him in his own hospital in the end he let "nature take its course."

E. B. STRAUSS, D.M., Hon.D.Sc., F.R.C.P.

The obituary of Dr. E. B. Strauss was published in the *Journal* of January 21 (p. 214).

Dr. J. L. BLONSTEIN, honorary medical officer of the Amateur Boxing Association of England and London, writes: In the obituary notice on the late Dr. E. B. Strauss no mention was made of his great interest in amateur boxing. Not only was he honorary medical officer to the Hanwell Club but he was also senior medical officer to the north-west division of the London Amateur Boxing Association

for many years. He was one of the consulting psychiatrists to the medical panel of the London A.B.A., and carried out a very interesting study on the psychiatric aspects of boxing. He will be greatly missed in amateur boxing circles.

Medico-Legal

THREATENED CONTEMPT PROCEEDINGS AGAINST PSYCHIATRIST

[FROM OUR LEGAL CORRESPONDENT]

A psychiatrist was recently required to attend before Mr. Justice Hilbery at the Surrey Assizes to answer for his conduct in the supervision of a sexual psychopath who entered his care under the terms of a probation order.

At a previous sitting of the Surrey Assizes a man aged 21 was convicted of certain sadistic sexual assaults on boys, which had caused considerable alarm to the police and to the public in the district where the man lived. A psychiatrist who gave evidence on behalf of the man said that, while he was not insane, he was suffering from a mental disturbance, albeit one to which the psychiatrist was not able to put a name. The psychiatrist said that if he were able to treat the man for a year he might be able to help him considerably.

The nature of the assaults, accompanied as they were by threats with a knife, caused the trial judge to doubt whether the public would be sufficiently protected by anything but a prison sentence. Subsequently counsel for the defence told the court that he was instructed that the psychiatrist would keep the convicted man in a closed ward.

The judge sentenced the prisoner to three years' probation, one of the terms of which was to be that he should remain for one year in a closed part of the hospital at which the psychiatrist was a consultant. The probation order, as drawn up by the Clerk of Assize, contained the condition of residence at the hospital for a year, but omitted to state that this should be in a closed part of the hospital. The psychiatrist was in court when sentence was passed.

The probationer was confined in the closed ward for three months, and then was allowed to play cricket and to take part in sporting fixtures at other hospitals as part of his rehabilitation. After about 4½ months he was allowed out with his mother to a near-by village on Wednesday afternoons, and, later, on Sundays also.

These excursions became known to the police. They reported the matter to the Clerk of Assize, with the result that the psychiatrist was called before the Assize judge in Court to make explanation. Proceedings for contempt of court were threatened, but the Court has now indicated that they will not be proceeded with.

Conflict of Intentions

If the probation order as drawn up by the Clerk of Assize had limited the condition of hospital residence expressly to residence in a closed ward, no doubt the subsequent trouble would not have arisen. However, it is doubtful whether the psychiatrist would have accepted the prisoner for treatment on those terms if he had considered the matter clearly. The root of the trouble seems to be that the Court was not fully acquainted with the intentions of the psychiatrist as regards treatment.

It is too often forgotten that punishment may be aimed at some or all of four possible objectives—namely, reform of the offender, retribution, prevention of the possibility of further offences by the offender, and deterrence of others. In many cases some of these objectives may be conflicting. It is for the Court, not for witnesses, to decide which objectives are to prevail. If a course of remedial treatment is recommended by a witness, he should make it clear what that treatment involves. Particularly if the Court has expressed concern about the preventive aspect of the sentence to be imposed, the witness should make it quite clear (if it be the case) that the treatment proposed involves progressive regaining of liberty and is to that extent inconsistent with the preventive aspect of punishment. The Court will then have the responsibility of choosing the course to be adopted.

It is submitted that probation with a condition of residence in a hospital is not generally the most suitable sentence when both treatment and confinement of the offender are required. The probation order gives the hospital authorities no power to detain the convicted person except in so far as such power arises out of his undertaking to the Court on the making of the probation order. A more satisfactory sentence would be a detention order under Part V of the Mental Health Act, 1959.

Medical Notes in Parliament

PEERS' VIEWS ON NEW CHARGES

[FROM OUR PARLIAMENTARY CORRESPONDENT]

The Lords staged their own censure motion on the increased Health Service charges on February 13 without resorting to the embittered controversy of the Lower House. Lady SUMMERSKILL made her first speech since becoming a life peeress on a subject which has long engaged her attention—"The outrageous exploitation of the sick by the drug firms"—and claimed that the well-to-do hypochondriac who pressed his doctor to prescribe expensive proprietary drugs would be left untouched by measures which would seriously affect the aged, the chronic sick, and children. Lord TAYLOR also entered the lists against what he called the parasitic packaging firms in the pharmaceutical industry, and demanded a Royal Commission to examine the industry. Lord AIREDALE was a lone voice in the whole dispute, crying out for free drugs for private patients. Lord GIFFORD alleged that amenity beds had become a gentlemanly racket, used largely on an old-school-tie basis for sick members of the medical profession and the nursing staff and their friends. He wanted them replaced by the "intermediate bed" on the Australian model.

Viscount HAILSHAM, answering for the Government the charges of shabby and shoddy proposals levelled by the Opposition peers, denied that the Government intended or regarded the new measures as an attack on the Health Service or the Welfare State. On the contrary, they were necessary to its healthy growth. In this he echoed the opinion expressed by Viscount AMORY, formerly Chancellor of the Exchequer, that the proposals were of a strictly limited nature, designed to secure that the Service should continue to develop, with the cost shared in approximately the same proportions as before between direct contributions and general funds. The motion was defeated by 79 votes to 27.

TERMINATION OF PREGNANCY BILL

The Medical Termination of Pregnancy Bill, introduced by Mr. KENNETH ROBINSON, has for all practical purposes run its course. The second reading debate on February 10 was adjourned because those who opposed it refused to let the Bill go into committee, and the chances of further progress for a private member's Bill which has attracted strong opposition are extremely remote. The Government, through Mr. D. RENTON, Under Secretary at the Home Office, raised no objection to the limited purpose of putting case law into statutory form, but did point out that the Bill* proposed important and controversial changes, extending the opportunities for legal termination of pregnancy, and gave rise to some serious and practical difficulties which would necessitate amendment if the Bill went further.

*See *Brit. med. J.*, February 4, p. 369.

AMENDING LAW ON SUICIDE

The Suicide Bill has been introduced into the House of Lords, and was given a first reading there on February 14. It contains only three clauses and two schedules. The first clause states simply: "The rule of law whereby it is a crime for a person to commit suicide is hereby abrogated." The second clause declares that "a person who aids, abets, counsels, or procures the suicide of another, or an attempt by another to commit suicide, shall be liable on conviction on indictment to imprisonment for a term not exceeding 14 years," and requires that proceedings shall be taken only with the consent of the Director of Public Prosecutions. The first of the two schedules sets out the Acts that are to be adapted to the new declaration of the law, and the second recites those that are to be repealed. No date has so far been fixed for the second reading of the Bill.

QUESTIONS IN THE COMMONS

Prison Sentence on Mentally Sick Person

Mr. KENNETH ROBINSON (St. Pancras, North, Lab.) asked the Minister of Health on February 13 why he was unable to provide hospital accommodation and treatment for Peter David Hastings, sentenced at Nottingham Quarter Sessions last week to five years' imprisonment, despite a medical report stating that he was mentally sick, and despite the Court's expressed willingness to make a hospital order under the Mental Health Act, 1959, had accommodation been available. Mr. ENOCH POWELL said he was inquiring into the circumstances in which the availability of suitable accommodation for this type of patient was not brought to the knowledge of the Court.

Mr. ROBINSON asked if the Minister would say, in the meantime, that when a man was mentally sick a prison sentence must never be accepted as a substitute for hospital treatment. Would he also confer with the Home Secretary to see what could be done to set right this injustice and get the man the hospital treatment he needed? Mr. POWELL: Before I say any more I would like to know the result of my inquiries into this case and see what, if anything, it throws up for action.

On February 20 Mr. ROBINSON asked the Minister of Health if he would make a further statement about the failure to provide hospital accommodation for Peter David Hastings. Mr. POWELL said he had every reason to think that suitable hospital accommodation was available if the doctor responsible had made due inquiry. The proper procedure in such cases was generally known.

School Dental Service

The MINISTER OF EDUCATION informed Mr. E. DU CANN (Taunton, Con.) on February 16 that discussions would take place shortly with local-authority and professional organizations with a view to securing improvements in the school dental service.

In-patient Costs in Hospitals

Mr. E. FERNYHOUGH (Jarrow, Lab.) asked the Minister of Health on February 14 what was the average weekly cost per in-patient in hospitals. Mr. POWELL gave him the following averages for each main type, taken from the hospital costing returns for 1959–60: *Acute hospitals*—non-teaching, £25 16s. 7d.; teaching (London), £36 9s. 7d.; teaching (provinces), £30 4s. 11d.; *long-stay hospitals*, £11 2s. 6d.; *hospitals for mental illness*, £7 12s. 8d.

Transistor Hearing-aids

Mr. J. SNOW (Lichfield and Tamworth, Lab.) invited the Minister on February 13 to remedy the deficiencies of the new transistor hearing-aid, which, he said, although having many advantages over the older model, was much less powerful and had no adjustment for pitch. Miss EDITH PITT, the Parliamentary Secretary, told him that a still more powerful earphone was being developed for the profoundly deaf. The transistor aid was not less powerful than the valve aid, but it had a different quality of tone, and that might be why some users found it less satisfactory. The possibility of modifying the tone was being investigated.

Doctors Dispensing Prescriptions

Mr. L. PAVITT (Willesden, West, Lab.) asked on February 20 how many doctors in the Health Service dispensed for their own patients; and how many items were so dispensed in each of the last three years. Miss PITT stated that the number was about 2,500 in England and Wales. The number of items probably exceeded 10,000,000.

Prescription Charge Refunds

Mr. B. MILLAN (Glasgow, Craigton, Lab.) asked the Minister of Pensions and National Insurance what proportion of applications to the National Assistance Board for refund of Health Service prescription charges over each of the past three years was granted; and what proportion was refused. Mr. J. BOYD-CARPENTER replied that it was not possible to answer this question in precisely the form in which it was asked, but in 1958 the total amount refunded by the National Assistance Board was £972,000, representing over 19 million prescription items; in 1959, £1,003,0000, representing over 20 million; and, in 1960, £1,066.000, also representing over 20 million. The numbers of applications rejected in these years were respectively about 3,000, 2,000, and 1,500.

Health Service Expenditure

Mr. W. HAMILTON (Fife, West, Lab.) asked the Minister of Health to what extent the increased expenditure on the Health Service in the last 10 years had been due to increased salaries and wages and increased costs, respectively. Mr. POWELL said this information was only available for the hospital service in England and Wales, and was: increase in expenditure, 1949–50 to 1950–60, £203m.; due to increases in salary and wage rates, £108m.; due to increases in price levels, £49m.

Vital Statistics

Influenza

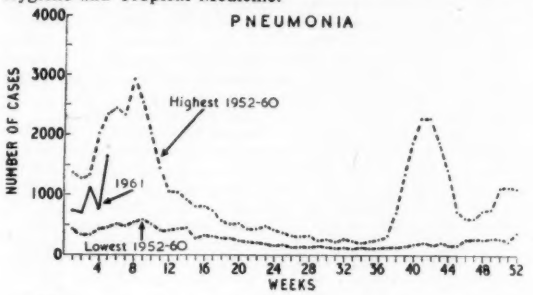
In the week ended February 11 there were 1,393 deaths from influenza in England and Wales, about 170 more than in the previous week and 35 times as many as in the corresponding week last year. Deaths from pneumonia (2,058) were a trifle fewer and deaths from bronchitis (1,809) rather more than in the preceding week. New claims for sickness benefit—though declining in the Midlands, in the East and West Ridings, and in the North-western region—were 10% higher than in the previous week. Though by February 11 influenza had declined in the Midlands and North, it had become more prevalent in southern parts of the country. Further isolations of influenza A2 virus were reported.

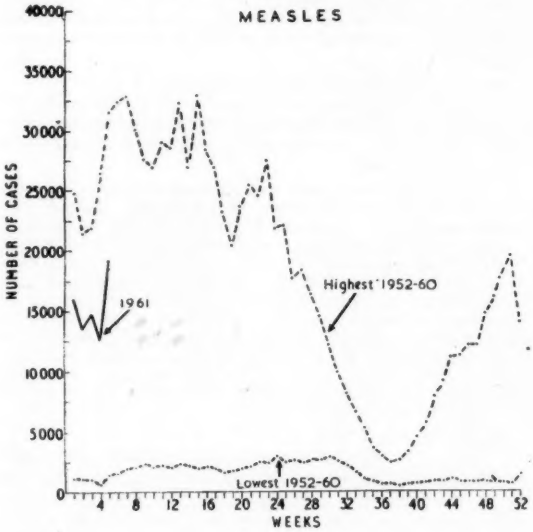
Births and Deaths in Northern Ireland

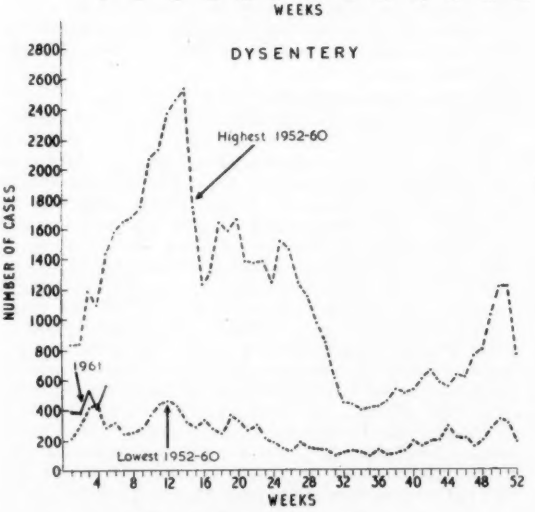
The birth rate in Northern Ireland during the third quarter of 1960 was 22.8 per 1,000 of the population—1.0 above the rate for the corresponding quarter of 1959 and 1.4 above the average of the five preceding third quarters. The infant mortality was 22 per 1,000 registered births, being 3 below the average of the corresponding quarters of the five preceding years; and the neonatal rate of 17 per 1,000 live births was 2 below the rate for the third quarter in 1959. The death rate was 9.3 per 1,000 of the population; this was 0.5 above the rate for the corresponding quarter of 1959 and 0.4 above the average of the five preceding years. Deaths from accidents numbered 130—11 more than in the third quarter of 1959: accidents in the home accounted for one-fifth and transport accidents for one-third of all deaths from accidents. Only 12 deaths were attributed to pulmonary tuberculosis, compared with 24 in the third quarter of 1959.

Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1952–60 are shown thus ------, the figures for 1961 thus ———. Except for the curves showing notifications in 1961, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.







Fatal Accidents in the U.S.A.

38,200 people lost their lives as a result of motor accidents in the U.S.A. in 1960. Accidents at home caused 27,500 deaths, and accidents at work 13,800. Public mishaps other than road accidents took 16,500 lives. Although the total number of fatal accidents was 1% up on the 1959 figure, the death rate from accidents—51.7 per 100,000 persons—was a little lower than in the previous year.—*New York Times*, February 17.

Infectious Diseases

Areas where the numbers of notifications were high in the latest two weeks for which figures are available.

	Week Ending Feb. 4	Week Ending Feb. 11
Dysentery		
Gloucestershire	18	**27**
Mangotsfield U.D.	0	**17**
Leicestershire	13	**20**
Leicester C.B.	9	**20**
Oxfordshire	3	**26**
Henley R.D.	0	**21**
Yorkshire West Riding	130	**198**
Bradford C.B.	14	**36**
Leeds C.B.	31	**50**
York C.B.	18	**41**
Measles		
Bedfordshire	361	**420**
Bedford M.B.	136	**221**
Derbyshire	412	**707**
Derby C.B.	132	**194**
Durham	934	**1,161**
Sunderland C.B.	285	**400**
Essex	1,284	**1,757**
Harlow U.D.	185	**299**
Hampshire	649	**985**
Southampton C.B.	192	**272**
Hertfordshire	520	**936**
Watford R.D.	81	**143**
Kent	755	**1,337**
Lancashire	1,776	**2,525**
Bolton C.B.	215	**239**
Manchester C.B.	184	**266**
Lincolnshire	340	**407**
London	2,008	**2,797**
Battersea	125	**214**
Islington	194	**207**
Wandsworth	232	**330**
Middlesex	826	**1,538**
Willesden M.B.	231	**341**
Northumberland	328	**474**
Newcastle upon Tyne C.B.	144	**200**
Nottinghamshire	517	**767**
Nottingham C.B.	196	**199**
Peterborough, Soke of	175	**171**
Staffordshire	489	**770**
Warwickshire	797	**1,664**
Birmingham C.B.	430	**919**
Coventry C.B.	196	**304**
Yorkshire East Riding	308	**642**
Kingston upon Hull C.B.	264	**481**
Yorkshire West Riding	1,517	**2,135**
Doncaster C.B.	195	**261**
Sheffield C.B.	146	**331**
Glamorganshire	664	**898**
Swansea C.B.	200	**268**
Paratyphoid Fever		
Cheshire	0	**3**
Hoylake U.D.	0	**3**
Food Poisoning		
Yorkshire West Riding	9	**26**
Sheffield C.B.	0	**25**
Diphtheria		
London	1	**2**
Islington	0	**2**
Warwickshire	0	**4**
Birmingham C.B.	0	**4**

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **February 4** (No. 5) and corresponding week 1960.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1961					1960				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	6	1	3	0	1	2	0	2	0	9
Dysentery	562	44	111	7	3	1,433	155	260	2	3
Encephalitis, acute	4	0		0		0	0		0	
Enteric fever:										
Typhoid	2	0	0	0		1	1	0	0	
Paratyphoid	1	0	0	0		0	0	1 (B)	0	
Food-poisoning	100	9	12	8		177	43	34	2	
Infective enteritis or diarrhoea under 2 years				11	24				7	23
Measles*	19,209	2008	307	393	508	1,580	44	26	12	6
Meningococcal infection	29	2	8	1	2	30	5	7	0	1
Ophthalmia neonatorum	24	4	3	0		25	4	4	0	
Pneumonia†	1,644	77	301	17	62	467	30	249	4	2
Poliomyelitis, acute:										
Paralytic	4	1	1	0		4	2	0	0	3
Non-paralytic	0	0	1			1	0	1		
Puerperal fever§	156	24	16	0		213	28	4	1	1
Scarlet fever	586	36	54	15	10	1,208	51	100	27	20
Tuberculosis:										
Respiratory	393	62	78	9		440	48	71	17	
Non-respiratory	52	7	6	1		47	2	10	6	
Whooping-cough	933	45	68	6	37	1,037	74	196	13	97

DEATHS	1961					1960				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	0	0	0	0	0	1	0	0	0	0
Dysentery	2	0		0		0	0		0	
Encephalitis, acute		0			0		0			0
Enteric fever	0	0	0	0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	16	0	1	1	0	15	33	0	0	0
Influenza	1,219	37	8	18	54	36	2	2	0	0
Measles		0	0	0	2		0	0	0	0
Meningococcal infection		1	0				0	1		
Pneumonia	2,060	142	62	61	36	682	68	34	29	11
Poliomyelitis, acute	1	0		0	0	0	0		0	0
Scarlet fever		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory	112	9	9	0	3	79	3	13	0	2
Non-respiratory		1		1	0		0	0	0	0
Whooping-cough	1	0	0	0	0	1	0	0	0	0
Deaths 0–1 year	419	37	29	12	20	341	33	29	9	15
Deaths (excluding stillbirths)	18,051	1379	806	261	379	11,176	912	690	136	173
LIVE BIRTHS	15,481	1294	1033	299	417	14,977	1276	1050	271	383
STILLBIRTHS	309	26	21			325	42	19		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

Rockefeller Foundation Grants

During the last quarter of 1960 Rockefeller Foundation grants amounted to $10,631,005; $3,115,689 of this sum went to the medical and natural sciences.

In the United Kingdom the Strangeways Research Laboratory, Cambridge, received a three-year grant of $20,000 for research in experimental biology, and the South-west Metropolitan Regional Hospital Board $23,000 till February, 1963, for research on the biochemistry of the nervous system under Dr. D. RICHTER. Medical Research Council, Neuropsychiatric Research Unit, Carshalton. Melbourne University, Australia, received a two-year grant of £A.50,000 for "an unique method," using Merino sheep, for studying the effect of adrenal hormones on salt and water balance. Among other overseas grants of medical interest were $240,420 over the next five years to the University of Guadalajara, Mexico, to modernize its faculty of medicine; a three-year grant of $47,000 to the French National Centre of Scientific Research for work on biochemical aspects of genetics; and three-year grants totalling $88,000 to the National Institute of Health, Tokyo, and Kyoto University, Japan, for virus research. The Foundation has increased support for its own work on arthropod-borne viruses and for its overseas consultant staff to $1,710,395. A grant was made to Adelaide University for research on kuru.

New Criminology Course at Cambridge

A postgraduate course in criminology has been established by the University of Cambridge, to be given by the Institute of Criminology. The first course will begin in October, and end in July, 1962.

The course, which leads to a diploma, will deal with all the major aspects of criminology, with particular reference to the development of criminological and penological thought and practice; the methodology of criminological research; the psychological and psychiatric context of criminal conduct; the sociology of crime; the principles of criminal law and procedure; the sentencing process, and the effectiveness of punishment and other methods of treatment; the non-institutional and institutional treatment of juvenile, young adult, and adult offenders; and certain aspects of the prevention of crime. Details and application forms are available from the Secretary, Institute of Criminology, 4 Scroope Terrace, Cambridge. The closing date for applications is May 15.

Queen Mother's Visit

H.M. THE QUEEN MOTHER, Chancellor of the London School of Hygiene and Tropical Medicine, visited the School on February 16. Among those receiving her was Dr. E. T. C. SPOONER, Dean of the School, and after the reception he conducted her round the various departments, where she was introduced to members of the staff and to students.

Hunterian Festival Dinner

The Hunterian Festival Dinner was held at the Royal College of Surgeons of England on February 14, the 233rd anniversary of John Hunter's birth, under the chairmanship of the senior vice-president of the College, Sir STANFORD CADE, the president, Sir Arthur Porritt, being in New Zealand. The large number of guests included the Mayor of Westminster, the French and Costa Rican Ambassadors, the Master of the Rolls (Lord Evershed), the Marquess of Salisbury, the High Commissioners for South Africa and Ceylon, the president of the Royal Society (Sir Howard Florey), the Minister of Health (Mr. Enoch Powell), Sir Henry Dale, and some of those captains of industry to whom the College is so deeply indebted for its physical expansion. After the Loyal Toasts and the silent homage to the memory of John Hunter, Sir HOWARD FLOREY proposed "The College" and Sir STANFORD CADE replied. "The Guests" was proposed by the junior vice-president, Professor DIGBY CHAMBERLAIN, Lord EVERSHED responding with the speech of the evening. As it had been his duty to find against the College in a recent Appeal Court case, he said, he thought it uncommonly nice of them to have invited him to the dinner. The Hunterian Orator (Sir RUSSELL BROCK) was thanked by Sir JAMES PATERSON ROSS, and Sir RUSSELL'S reply

ended an enjoyable evening. A summary of the Oration will be found at p. 584.

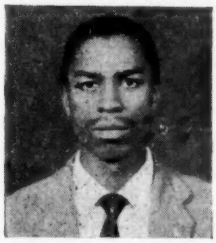
M.R.C. Fellowships in Clinical Research

The Medical Research Council invites applications for a further series of Fellowships in clinical research, tenable at centres in the United Kingdom during the academic year 1961–2. These Fellowships are open to suitably qualified medical or dental graduates who are British subjects resident in the United Kingdom and who desire to prepare themselves for a career in clinical research. Details and application forms may be obtained from the Secretary, Medical Research Council, 38 Old Queen Street, London S.W.1, to whom applications should be sent as soon as possible, in any event not later than March 23.

"Current Medical Research"

The Medical Research Council has issued a reprint of the articles in the *Report of the Medical Research Council for the Year 1958–59*. These are brief but authoritative reviews of some of the more important recent findings of medical or biological research. For the year in question the reviews include: Occupation and Coronary Heart Disease; Studies on the Chemotherapy of Tuberculosis in East Africa and India; Clean Air in Operating Theatres; Human Population Genetics; Chromosome Abnormalities and Disease in Man; New Applications of Electron Microscopy; the Structure of Viruses; the Structure of Muscle in Relation to the Mechanism of Contraction; Interferon: the Prospects for an Anti-viral Agent in Man; the Arthropod-borne Viruses; the Plasma Kinins; and Some Factors in the Problem of Inattention. (H.M.S.O., price 3s. 6d. net.)

First Matabele African Doctor



Dr. SIPHO ZWANA, who is the first Matabele to qualify as a doctor, has also become the first African to join the medical staff at Mpilo Hospital, Bulawayo, Southern Rhodesia. Dr. Zwana, who is the son of a Methodist minister, is aged 27 and qualified at the University of Natal, Durban.

"Revue Française d'Allergie"

The new *Revue Française d'Allergie*, journal of the Société Française d'Allergie, will be published quarterly at a cost of N.F.28 a year. The editor is Dr. P. BLAMOUTIER, president of the Society, and the first issue contains an article by Professor PASTEUR VALLERY-RADOT, who founded the society in 1947, on the part played by France in the study of allergic disorders. Inquiries should be addressed to the publishers, L'Expansion Scientifique Française, 15 rue St.-Benoit, Paris 6, France.

Whole-time Consultants Association

The following officers have been elected: *president*, Dr. A. A. CUNNINGHAM; *hon. treasurer*, Dr. R. M. MAYON-WHITE; *hon. secretary*, Dr. J. WALTER.

In Brief

The sixteenth World Health Assembly has been invited to meet in Moscow in 1963.

Grants, Gifts, and Bequests

Sir ARTHUR THOMSON, formerly dean of the medical school of Birmingham University, has donated a sum of money to the Faculty of Medicine there to inaugurate a "Dean's Fund."

The Simon Population Trust has been left £15,000 by the late Lord SIMON OF WYTHENSHAWE. The object of the trust is to promote study of the problems of world population and particularly of family planning.

People in the News

Mr. T. HOLMES SELLORS was made an Honorary Member of the Association of Surgeons of India at their annual meeting in December, 1960.

COMING EVENTS

Royal College of Physicians, Edinburgh.—Symposium, "Some Aspects of Renal Disease," March 25, 9.15 a.m., Hall of College, 9 Queen Street. Programme includes two Sydney Watson Smith lectures: Dr. J. S. ROBSON (Edinburgh), "Patterns of Renal Insufficiency," followed by panel discussion, "Renal Failure and its Management," and Dr. J. P. MERRILL (Boston, Mass.), "Renal Transplantation," followed by panel discussion on same subject. Three speakers will discuss "The Nephrotic Syndrome" under the headings of "Light and Electron Microscopy of the Kidney," "Steroid Therapy," and "Immuno-chemical Mechanisms and their Possible Application in Steroid Therapy." See advertisement p. 60 for details of admission. Applications by March 4.

7th James Yearsley Memorial Lecture.—Mr. J. D. K. DAWES, on behalf of Dr. LOUIS VERHOEVEN, "The Examination of a Chronic Ear," March 3, 5 p.m., Royal Society of Medicine, 1 Wimpole Street, London W.1.

British Tissue Culture Association.—Symposium, "Cell-specific Proteins," March 4, 9.30 a.m.–5 p.m., Auditorium, Wellcome Building, Euston Road, London N.W.1. Organizing Secretary: Professor C. E. LUMSDEN, Department of Pathology, School of Medicine, Leeds 2.

Birmingham Medical Institute.—Annual dinner at Institute, March 5, 7 p.m. Tickets, 30s. per person, from Dr. H. E. THOMAS, West Heath Hospital, Rednal Road, Birmingham 31. (KINgs Norton 4191.)

Oliver-Sharpey Lectures. — Professor E. P. SHARPEY-SCHAFER, "Venous Tone," March 7, 9. See advertisement p. 60.

Institute of Dermatology.—Semi-permanent exhibition, March 8–30, by Dr. A. D. PORTER and Dr. I. A. MAGNUS. "Effects of Light on the Skin." St. John's Hospital for Diseases of the Skin, Lisle Street, London W.C.2.

Zoological Society of London.—Symposium, "Aspects of Disease Transmission by Ticks," March 8, 10.30 a.m., Meeting Room, Zoological Society of London, Regent's Park, London N.W.1. Details from secretary at that address.

Aberdeen University Department of Surgery.—Professor A. W. KAY, "The Changing Outlook—the Surgical Treatment of Duodenal Ulceration," March 10, 5 p.m., Foresterhill, Aberdeen.

British Postgraduate Medical Federation.—Weekend course on general medical subjects, March 11, 12, Joyce Green Hospital, Dartford. Details from Dr. H. C. CALVEY, Chest Clinic, West Hill Hospital, Dartford, Kent.

Institute of Urology.—Week-end course, "Essentials of Urology," March 17–19. See advertisement p. 60.

R.S.M. (Section of Experimental Medicine and Therapeutics) and Renal Association.—Joint meeting, March 17, 2.30 p.m., Royal Society of Medicine, at which participants in Ciba Foundation symposium on "Clinico-pathological Significance of Renal Biopsy" will discuss proceedings of Symposium. Speakers: Professor A. R. RICH (Baltimore), Dr. R. L. VERNIER (Copenhagen), Professor J. HAMBURGER (Paris), Dr. C. BRUN (Copenhagen), Professor D. P. EARLE (Chicago), Professor R. KARK (Chicago). Those wishing to attend should either accompany or bear introduction from Fellow of R.S.M. or member of Renal Association.

Cambridge University Postgraduate Medical School.—Symposium, "The Adrenal and Anaesthesia," March 18, 10.30 a.m., Radiotherapeutic Centre, Addenbrooke's Hospital, Cambridge. Details from the secretary, Medical School, Tennis Court Road, Cambridge.

Faculty of Radiologists.—Courses for D.M.R.D. and D.M.R.T. (R.C.P.Lond., R.C.S.Eng.), October, 1961. See advertisement p. 60.

NEW ISSUES OF SPECIALIST JOURNALS

The journals listed below are obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London W.C.1.

BRITISH JOURNAL OF VENEREAL DISEASES

Venereal Disease and the Public Health. G. L. M. McElligott.
Age Group of Patients with Infectious Venereal Disease, 1957 and 1958 British Co-operative Clinical Group.
Country of Origin of Patients Attending Venereal Disease Clinics: A Study of 138,626 Cases. British Co-operative Clinical Group.
Transportation of Material for the Culture of the Gonococcus. A. Reyn, B. Korner, and M. W. Bentzon.
Results of Penicillin Therapy in Syphilitic Primary Optic Atrophy. P. Segal, B. Janiszewska-Geldner, and J. Leonowicz-Michniowska.
Tabetic Spinal Arthropathy: Two Cases with Motor Symptoms Due to Root Compression. C. D. Alergant.
Unusual Subjective Reaction Following Dihydrostreptomycin: Report of Seven Cases. J. Oliver Doyle.
Bilharzial Cystitis. A. I. Morrison.
Bilharzia in a Patient with Gonorrhoea. R. M. Warren.
Book Reviews.
Abstracts.
Index.

Volume 36, No. 4. (Quarterly; £3 annually.)

MEDICAL AND BIOLOGICAL ILLUSTRATION

Frontispiece.
Gargoylism. Derek Martin.
A Nomogram for Colour Light Balancing Filters. C. S. McCamy.
Further Advances in Fluorescence Colour Photography. W. D. Tredinnick.
Some Uses of Thorotrast. G. E. H. Foxon.
The Use of Ultrasound in Diagnosis. Marjorie J. Hill and Ian McColl.
Practical Techniques in Rapid Sound Film Production. Herbert A. Fischler.
Avdi Partem Alteram.
Equipment and Methods:
Baldwin Photometer Type M.N.D.
Polaroid Land 4×5 Film Holder.
A Simple Method of Recording Ouchterlony Plates.
I.C.R.F. Cinemicroscope MK 2.
Fluorescent Blackboard Chalk.
Measuring Magnifier.
All Purpose Head and Chin Rest.
Abstracts.
Book Reviews.
Motion Pictures.
Reports and Proceedings.

Volume 11, No. 1. (Quarterly; £3 annually.)

BRITISH JOURNAL OF OPHTHALMOLOGY

Reaction of Animal Eyes to Sanguinarine and Argemone Oil. G. C. Dobbie and M. E. Langham.
Experimental Hemeralopia Uncomplicated by Xerophthalmia in Macacus rhesus. F. C. Rodger, A. D. Grover, and A. Fazal.
Uveitis and Urogenital Disease in the Male. R. D. Catterall and E. S. Perkins.
End-to-side Anastomosis for Obstruction of the Naso-lacrimal Duct. R. A. Burn.
Glaucoma Treated with Daranide. M. H. Luntz.
Pathology and Treatment of Non-cicatricial Entropion by the Method Proposed by Wies. O. O. F. Flooks.
Cataract Extraction by Expression. L. Lurie.
Dacryocystorhinostomy. R. P. Sarda, O. P. Kulshrestha, R. N. Mathur.
Pseudo-glioma Due to Larval Choroidal-retinal Granulomatosis. W. Harris.
Delayed Local Metastasis in a Choroidal Melanoma. R. J. McWilliam.
Intra-ocular Cysticercus. L. Meyerson and B. T. Pienaar.
Bilateral Intra-ocular Cysticerci. E. Balakrishnan.
New Use for Old Mirrors. A. I. Friedmann.
Reviews.
Notes.

Volume 45, No. 2. (Monthly; £6.)

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday, February 27

MANCHESTER MEDICAL SOCIETY: SECTION OF ODONTOLOGY.—At Manchester Dental Hospital (Lecture Room), 5 p.m., Mr. G. Colman: Some Antiseptics Used in Oral Surgery.

MANCHESTER MEDICAL SOCIETY: SECTION OF GENERAL PRACTICE.—At Manchester Medical School (Large Anatomy Theatre), 9 p.m., Mr. G. D. Jack: Cough.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Professor I. G. W. Hill: Some Problems in the Management of Resistant Heart Failure.

Tuesday, February 28

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Dr. A. G. Spencer: Hypertension and Unilateral Renal Disease—the Selection of Patients for Surgery.

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. J. A. Dudgeon: Virus Infections I.

ROYAL COLLEGE OF SURGEONS OF ENGLAND.—4.15 p.m., Arnott Demonstration by Dr. R. McP. Livingston: Conjoint Twins.

ROYAL STATISTICAL SOCIETY: MEDICAL SECTION.—At London School of Hygiene and Tropical Medicine (Manson Theatre), 5.30 p.m., Dr. Roy M. Acheson: Problems in the Measurement of the Maturity of the Growing Skeleton.

ST. MARY'S HOSPITAL MEDICAL SCHOOL.—At Lecture Theatre, Wright-Fleming Institute, 5 p.m., Dr. Michael Feiwel: Pruritus Vulvae.

WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY.—5.30 p.m., Dr. G. Parsons-Smith: clinical demonstration in neurology.

Wednesday, March 1

BIRMINGHAM MEDICAL INSTITUTE: MIDLAND MEDICAL SOCIETY SECTON.—At 36 Harborne Road, Edgbaston, 8.30 p.m., Mr. W. J. Dempster: Anuria Following the Transplantation of Kidneys.

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. H. Haber: Cytodiagnosis.

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Mr. L. L. Bromley: Pulmonary Embolism.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—5.30 p.m., Dr. I. Friedmann, Dr. D. A. Osborn and Dr. A. L. Jeanes: clinical pathological conference.

INSTITUTE OF UROLOGY.—4.30 for 5 p.m., Dr. A. R. Harrison: Metabolism and Stones.

LIVERPOOL MEDICAL INSTITUTION.—Visit to Manchester Medical Society.

MANCHESTER MEDICAL SOCIETY.—At Manchester Medical School, 4.30 p.m., joint meeting with Liverpool Medical Institution. Dr. A. J. Robertson: Pneumoconiosis Due to Tin Oxide. Dr. F. P. Hudson: The Dumb Blonde is My Baby; Being the Story of Phenylketonuria in Liverpool.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—2 p.m., Professor R. A. Willis: Examination of the Supposed Increase of Bronchial Carcinoma and of the Validity of its Histological Typing.

Thursday, March 2

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Dr. J. D. N. Nabarro: Oral Hypoglycaemia Agents.

ROYAL COLLEGE OF SURGEONS OF ENGLAND AND INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—At Royal College of Surgeons of England, 5.30 p.m., Otolaryngology Lecture by Professor L. P. Garrod: Principles of Antibiotic Therapy in Surgery.

ST. ANDREWS UNIVERSITY.—At Physiology Department Lecture Theatre, 5 p.m., Mr. John Charnley: Lubrication of Animal Joints in Relation to Orthopaedic Surgery

ST. GEORGE'S HOSPITAL MEDICAL SCHOOL.—5 p.m., Dr. Maurice Partridge: postgraduate demonstration in psychiatry.

UNIVERSITY COLLEGE LONDON: DEPARTMENT OF BIOCHEMISTRY.—At Physiology Theatre, Gower Street, W.C., 5 p.m., public lecture by Dr. W. J. Whelan: Recent Advances in the Chemistry and Biochemistry of Glycogen and Starch—(2) Enzymic Degradation and Glycogen-storage Diseases.

Friday, March 3

CAMBRIDGE UNIVERSITY: SCHOOL OF CLINICAL RESEARCH AND POSTGRADUATE MEDICAL TEACHING.—At Radiotherapeutic Centre, 4.15 for 4.30 p.m., Dr. J. M. Walshe: Radio Copper Studies in Wilson's Disease.

● INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. F. R. Bettley: clinical demonstration.

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. R. V. Gibson: cardiological demonstration.

MEDICAL ELECTRONICS DISCUSSION GROUP.—At Institution of Electrical Engineers, Savoy Place, London W.C., 5.30 for 6 p.m., discussion to be opened by Mr. H. B. Morton and Mr. H. R. A. Townsend: "Clinical Value of E.E.G. Recording" and "Present Trends in General Purpose E.E.G Recorders."

METROPOLITAN EAR, NOSE, AND THROAT HOSPITAL.—At Royal Society of Medicine, 5 p.m., James Yearsley Memorial Lecture (speaker, Mr. J. D. K. Dawes, on behalf of Dr. Louis Verhoeven): Examination of a Chronic Ear.

PLYMOUTH MEDICAL SOCIETY.—At North Friary House, 8.30 p.m., short papers by Dr. G. B. Carter, Dr. T. L. Chester-Williams, Mr. I. Sutherland-Jones, and Dr. B. J. Peck.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—(1) 10 a.m., Mr. B. H. Page: Prostatic Surgery. (2) 4 p.m., Dr. F. S. Cooksey: Management of Disability.

Saturday, March 4

BRITISH TISSUE CULTURE ASSOCIATION.—At Auditorium, Wellcome Building, Euston Road, London N.W., 9.30 a.m., symposium: Cell-specific Proteins.

CAMBRIDGE UNIVERSITY MEDICAL SCHOOL.—At Norfolk and Norwich Hospital, symposium: Medical Aspects of Life Insurance and Hypertension. 11 a.m., Medical Aspects of Life Insurance. To be opened by Dr. K. A. Latter and Mr. Russell Mallett, F.I.A. 2.30 p.m., Modern Management of Hypertension. To be opened by Dr. W. A. Oliver, Dr. R. S. Thorpe, and Mr. A. B. Birt.

MIDLAND THORACIC SOCIETY.—At Birmingham Medical Institute, 36 Harborne Road, Edgbaston, 3 p.m., Dr. A. John Robertson: Investigation of Stannosis.

SHEFFIELD REGIONAL PSYCHIATRIC ASSOCIATION.—At Mapperley Hospital, Nottingham, 11 a.m., Professor G. M. Carstairs: Epidemiology of Mental Disorders—Its Scope and its Methods.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Chamberlain.—On February 10, 1961, at Queen Charlotte's Hospital, London W., to Jocelyn (formerly Kerley) and Geoffrey Chamberlain, F.R.C.S., a sister for Christopher and Marie—Hilary Rosalind.

Jacoby.—On December 22, 1960, in New York City, U.S.A., to Thelma, wife of Dr. M. G. Jacoby, a sister for David—Wendy Ellen.

Weston.—On February 10, 1961, at University College Hospital, Jamaica, to Ann (formerly Daniels) and Peter Weston, F.R.C.S., a sister for Theo and Cecilia.

DEATHS

Burkitt.—On February 1, 1961, Frederick Thomas Burkitt, M.D., D.M.R.E., of Wimbledon, London S.W., aged 69.

Butler.—On February 6, 1961, at Taunton, Som., Malcolm Boyce Butler, M.B., B.S., aged 28.

Carter.—On February 5, 1961, at 49 Bainbridge Road, Sedbergh, Yorks, Arthur Humton Carter, M.D., aged 87.

Chalmers.—On February 6, 1961, at Duke of York Home, Bradford, William Chalmers, M.B., Ch.B.

Harrison.—On January 31, 1961, at Hollins House, Winwick, Warrington, Lancs, Geoffrey John Harrison, L.R.C.P.&S.I. & L.M., D.P.M.

Macphail.—On January 31, 1961, at Holm House, Carloway, Isle of Lewis, Norman Macphail, M.B., Ch.B., late of 24 Holme Lane, Sheffield, Yorks.

Scott.—On January 31, 1961, Alexander Scott, M.B., Ch.B., of Belmont, Jedburgh, Roxburghshire.

Sellars.—On January 30, 1961, at his home, 133 Preston New Road, Blackburn, Lancs, John Aloysius Sellars, M.B., B.Ch.

Sharpley.—On January 16, 1961, at his home, 8 Merton Court, Merton Road, Southsea, Hants, Thomas Stoney Sharpley, M.R.C.S., L.R.C.P., aged 78.

Steele.—On January 28, 1961, Patrick Steele, M.D., F.R.C.P.Ed.

Any Questions ?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Phenothiazine Derivatives

Q.—*Each day new drugs appear that are phenothiazine derivatives or allied drugs. We hear the terms monoamine oxidase inhibitor, psychotropic, ataractic, mood elevator, tranquillizer, hibernator, psychic energizer, thymoleptic, anti-depressant, and neuroleptic. The terms sedative, hypnotic, and anti-convulsant are easily understood. Could somebody please classify these drugs under their actions?*

A.—One has considerable sympathy with the feelings of the doctor who has posed this question. The rapidity with which new drugs with actions on the nervous system are being produced, the variety of terms which are applied to these substances, and the claims which are made for them by the manufacturers are indeed bewildering.

The problem began when it was found that certain of the antihistamine drugs had a mild sedative or calming effect, but that even in large and lethal doses they did not cause more than drowsiness. In this respect they differ from the usual sedatives and hypnotics, all of which cause sedation with small doses, sleep with moderate doses, and unconsciousness and finally death from respiratory depression with large doses. The term *tranquillizer* was therefore applied to drugs which had this action of causing sedation and tranquillity in doses which did not cause much drowsiness.

The tranquillizers can be divided into two main groups which correspond roughly to their use in psychiatry. The first group are those which are used mainly in the treatment of the psychoses such as schizophrenia, mania, senile dementia, and behaviour disorders in children. In general medicine they are of value in the treatment of nausea and vomiting and hiccup, and they potentiate the action of analgesics. This group includes the phenothiazines, promazine and its derivatives—for example, "stemetil" (prochlorperazine), "fentazin" (perphenazine), and "stelazine" (trifluoperazine). Their action and uses were recently well reviewed in this journal by Rees.[1] Reserpine, which is not a phenothiazine derivative, also belongs to this group.

The second group of tranquillizers are used mainly in the treatment of neuroses; examples are meprobamate, benactyzine, and "librium" (methamino-diazepoxide). The evidence that the drugs in this group are any more effective than small doses of well-established sedatives such as phenobarbitone or amylobarbitone is not convincing.

The term *ataractic* is a very old one and implies that the substance described frees the mind from external disturbances and produces either a sensation of pleasant detachment or one of stoical indifference. Recently the term has been used either as synonymous with tranquillizer[2] or specifically to refer to "atarax" (hydroxyzine). Some of the tranquillizers, notably chlorpromazine, have the additional property of lowering body temperature and they are therefore used by anaesthetists as adjuncts in the induction of hypothermia for surgical operations. When used in this way they may be referred to as *hibernators*.

Monoamine oxidase inhibitors are drugs which act by blocking the enzyme monoamine oxidase. This enzyme destroys certain important amines in the body, of which the best known are noradrenaline and 5-hydroxytryptamine (serotonin). Several well-established drugs such as ephedrine and cocaine have this action, but in clinical practice the name monoamine oxidase inhibitor is usually applied to more recently discovered hydrazine derivatives of which probably the best known are "marsilid" (iproniazid), "nardil" (phenelzine), and "niamid" (nialamide). It is believed that these drugs have an anti-depressive and euphoric action by virtue of the fact that they prevent the inactivation of noradrenaline and 5-hydroxytryptamine in the brain. They have also been recommended for the treatment of angina pectoris and rheumatoid arthritis.

Any drug which is effective in the treatment of depression is an *anti-depressant*, but the term is not a very useful one from the therapeutic point of view because there are so many varieties of depression and these require different types of drugs.[3] Neurotic depression is often helped by the amine-oxidase inhibitors and it was to iproniazid that the term "*psychic energizer*" was applied.[4] The amine-oxidase inhibitors, however, are of little value in endogenous depression, for which "tofranil" (imipramine) is at present probably the drug of choice. The exact pharmacological action of this drug has not yet been determined; it is not a tranquillizer and it is not an amine-oxidase inhibitor. Therefore some term descriptive of its clinical activity is required and "*mood-elevator*" and "*thymoleptic*" have been used. The latter term is unfortunate, as it will suggest to many an action upon the thymus gland, and the idea that the thymus has anything to do with the mind belongs to the dark ages of medicine.

The other terms, *psychotropic* and *neuroleptic*, are non-specific and can be used to refer to any drug which has an affinity for the mind or acts upon the nervous system. The phrase, "broad-spectrum psychotropic drug," is sometimes used. This seems to imply that the substance so described will calm the anxious or agitated patient and elevate the mood of the depressed patient. Such terms have little to commend them and cannot but be confusing to anyone who is not familiar with current trends in the therapy of psychiatric disorders. Until more is known about the pharmacological action of these new preparations we shall probably have to put up with these and other descriptive phrases which seem to delight the drug manufacturers and their representatives but only bewilder the average medical practitioner.

REFERENCES

1 Rees, L., *Brit. med. J.*, 1960, **2**, 522.
2 Lewis, J. J., *An Introduction to Pharmacology*, 1960. Livingstone, Edinburgh.
3 *Brit. med. J.*, 1960, **1**, 178.
4 Loomer, H. P., Saunders, J. C., and Kline, N. S., *Psychiat. Res. Rep. Amer. psychiat. Ass.*, 1957, No. 8, 129.

Radioactivity of Milk

Q.—*Is the level of radioactive substances in milk steadily rising in spite of seasonal fluctuations? If so, should the intake of milk of a child who normally drinks at least three pints (1.7 litres) a day be reduced?*

A.—The concentration of strontium-90 in milk is measured regularly by the Agricultural Research Council. Its latest report (A.R.C.R.L. 3, H.M.S.O., London) indicates that in 1959 the levels were some 40% greater than in 1958, and followed the pattern of the *rate* of fall-out of strontium. Since the *rate* of fall-out has decreased progressively since mid-1959 a fall in the levels of milk can be predicted during 1960. Even at the concentrations current in 1959 (an average of barely 10 $\mu\mu$c/g. Ca) there is no reason to reduce a child's intake of milk. The M.R.C. Committee's second report[1] discusses the permissible levels of strontium-90 in bones of children.

REFERENCE

1 *The Hazards to Man of Nuclear and Allied Radiations: A Second Report to the Medical Research Council*, 1960. H.M.S.O., London.

Flea Infestation

Q.—*I regularly become infested with fleas during my rounds in the early or mid-winter. How can I rid myself of the infestation and prevent infestation? Also, how can the patients and houses concerned be disinfested?*

A.—Flea "infestations" of the body are only temporary, in that these insects do not breed on the host (like lice), and after a meal they usually drop off to lay their eggs. The young stages (larvae and pupae) are found under dust and debris near the sleeping place of the host. Thus it is

the bedroom rather than the body which is infested by the human flea, and permanent infestations are most unlikely to develop in houses with regular and thorough cleaning.

Occasional temporary infestations of the clothing are, nevertheless, a disagreeable liability of doctors who visit houses with low standards of hygiene. D.D.T. (10%) or *gamma* B.H.C. (0.5%) powder liberally applied to the under garments ought to kill any fleas acquired by the wearer; if speed of action is required, a good brand of synergized pyrethrum powder might be better. Alternatively (or in addition), a repellent might be used. The most effective would be dimethyl phthalate (D.M.P.), which should be smeared undiluted over trouser ends and socks and perhaps sleeve ends. It is colourless and odourless and should be undetectable; but it should not be allowed to come in contact with plastic materials.

To eradicate infestations in the home, thorough cleansing of bedrooms is essential to destroy the larvae in the breeding site. This should be combined with attacks on the adult fleas by use of powder insecticides applied to clothing or bedding. Finally, it is worth making sure that human fleas are really involved. Temporary infestations may be due to dog or cat fleas breeding in the neglected sleeping place of a household pet. Specimens will be identified by the Public Health Laboratory Service, Entomological Reference Laboratory, or by the British Museum (Natural History).

O from A and A

Q.—*If the parents of a child are blood group A can the child be blood group O?*

A.—Persons of blood group A may either be homozygous for the gene or heterozygous. In the first case they carry two blood group A genes, and, if two such people marry, all their offspring can carry only blood group A. If two heterozygotes (AO) marry they will, in the laboratory, give a positive test for blood group A, but, since they both also carry the blood group O, there is a chance of 1 in 4 for their child to be blood group O (OO). Other children may have the blood group A, and will either be homozygous (AA) or heterozygous (AO). It is therefore fully possible for two parents of blood group A to have a child with blood group O.

Genetic Risks of Radiology

Q.—*Is there any chance of foetal anomalies occurring in a child fathered by a man who has had an intravenous pyelogram performed?*

A.—The chances of a foetal anomaly occurring in a child fathered by a man who has had an intravenous pyelogram performed are, in the light of our present knowledge, nil.

Oculent. Hyd. Ox. Flav.

Q.—*In what way has oculent. hyd. ox. flav., B.P., been altered?*

A.—Eye ointment of yellow mercuric oxide (oculent. hyd. ox. flav., *B.P.*) was first included in the 1932 edition of the *British Pharmacopoeia*, although the 1914 edition contained a formula for ointment of yellow mercuric oxide which contained 2% of the active ingredient. From 1932 until 1953 the *B.P.* formula for this eye ointment was yellow mercuric oxide 1% in a sterilized base containing wool fat 10% and of yellow soft paraffin 90%.

The 1958 edition of the *British Pharmacopoeia* altered the base to liquid paraffin 10%, wool fat 10%, and yellow soft paraffin 80%. This alteration was made as some ophthalmologists considered that the old base was too stiff. The change in the consistency of the base is unlikely to have any significant effect on the therapeutic action of the ointment. In recent editions permission has been given for the prescriber to vary the amount of yellow mercuric oxide in the ointment, but, if no strength is stated, the 1% preparation must be supplied.

Polio Vaccination Late in Pregnancy

Q.—*When poliomyelitis vaccination has been omitted early in pregnancy is there any contraindication to carrying it out in the last two months?*

A.—There is no reason why polio vaccine should not be given in the last two months of pregnancy. It would mean that the mother would be able to have only two doses of vaccine (presumably killed, Salk-type vaccine), and therefore that the baby would receive a limited amount of maternally transmitted antibody. This would probably not last for more than a few months and give only a slight degree of protection, but otherwise no harm would accrue to either mother or child.

NOTES AND COMMENTS

Emergency Equipment in Ambulances.—Dr. J. A. SCOTT (Medical Officer of Health, London County Council) writes: I was interested to read the answer to a question ("Any Questions ?" November 26, p. 1615) about the emergency surgical equipment which ought to be carried in ambulances. The answer included an expression of the view that "there is no need for ambulances to carry chloroform, intravenous anaesthetics, morphia or adrenaline." The questioner had in mind "a country area where roads are good and there are up-to-date hospitals," and the view that in such an area the carrying of these drugs in ambulances is unnecessary would presumably be even more strongly held in respect of an urban area where roads were no less good and hospitals more plentiful. It would therefore be of interest to mention that our experience in London does not entirely support this view. Each ambulance in the accident section of the London ambulance service carries a small supply of morphine, adrenaline, nikethamide, and chloroform, and, although the calls for these by doctors present at the scenes of accidents are not very numerous, they do occur sufficiently often to confirm my opinion that the ready availability of these drugs to a doctor dealing with a casualty is a useful additional facility which an emergency ambulance service may reasonably be expected to provide. London is, of course, particularly well served in having over 50 hospitals which are prepared to accept casualties of all kinds taken in by ambulance at any hour of the day or night, and the average time which elapses between the time when the call for an ambulance is received and the time of the arrival of the casualty at hospital is about 20 minutes, but, even under these very favourable conditions, a call for one of the drugs mentioned—most often morphine—is received on an average of about once a fortnight, and I would have thought that in areas where considerably longer journeys to hospital are involved the need for these drugs would be rather greater. It is to be remembered, moreover, that however near a casualty-receiving hospital may be to the scene of an accident it may be inadvisable—or indeed impossible—to move the casualty for a considerable time—for example, if he is trapped under debris or in a wrecked vehicle or machinery or in some position difficult of access, such as a lift shaft or a high building under construction, and it is in situations such as these that an injection can often be given by a doctor who happens to be present but has not his own equipment with him.

Collected Articles from the "British Medical Journal"

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